frontiers | Research Topics

Case reports in dermatology

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Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-3430-4
DOI 10.3389/978-2-8325-3430-4

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Case reports in dermatology

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Citation
Recke, A., Hashimoto, T., eds. (2023). *Case reports in dermatology*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3430-4

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frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 23 August 2023
DOI 10.3389/fmed.2023.1269802

OPEN ACCESS

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RECEIVED 30 July 2023
ACCEPTED 14 August 2023
PUBLISHED 23 August 2023

CITATION
Recke A and Hashimoto T (2023) Editorial: Case reports in dermatology.
Front. Med. 10:1269802.
doi: 10.3389/fmed.2023.1269802

Editorial: Case reports in dermatology

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KEYWORDS

case report, autoimmune bullous diseases of the skin, rare diseases, allergy, drug reactions, autoinflammation, hereditary angioedema

Editorial on the Research Topic
Case reports in dermatology

Introduction

Dermatology relies heavily on visual impressions, and dermatological residents need exposure to a variety of clinical pictures and presentations to develop their diagnostic skills. Moreover, the abstract immunological processes become more tangible and understandable when they are manifested on the skin. As such, case reports that feature unique or atypical visual characteristics are particularly valuable in Dermatology. Yet, it's crucial to emphasize that training budding dermatologists isn't solely about visual interpretations from case reports. The tactile nuances and three-dimensional aspects of skin conditions are just as vital, for some skin changes are better discerned through touch than sight alone. That said, our visual perception, augmented by tools like reflected-light microscopy, empowers us to discern intricate textures and color nuances, elements that two-dimensional images struggle to capture fully.

Case reports are typically considered the lowest level of clinical evidence (1). Although they require some clinical experience and specificity, they do not involve study design, experimentation, or targeted data collection. Because case reports are usually only published if they describe novel or unusual cases, they are often subject to bias. However, as a format, case reports do not limit themselves to a small number of variables, unlike randomized interventional trials, and can represent individual cases in their multifaceted nature.

To increase the transparency and quality of case reports, guidelines such as the CARE guideline have been developed (2). Some journals require adherence to these guidelines when submitting case reports, which can aid in the formal review process. However, Frontiers in Medicine does not mandate adherence to any specific guidelines for case reports.

While case reports do not have to be new or unusual to be published in Frontiers in Medicine, their scientific value may be reduced if there are studies with stronger evidence available. For example, if there are randomized controlled trials on the use of drug A for disease B, a case report on the same topic may not be necessary. The situation with the SARS-CoV2 pandemic has changed significantly over the past 3 years, with a wealth of new knowledge gained. As a result, case reports on SARS-CoV-2 that may have been interesting in the early days of the pandemic could now be obsolete or problematic. Ultimately, case reports should address gaps in medical knowledge, initiate discussions on diagnosis and treatment, and highlight areas where needs are unmet.

Frontiers does not impose a rate for rejections. Rejections are primarily justified on scientific grounds. In the case of this Research Topic, only 21 of 35 submitted case reports—and one correction—were finally accepted, which corresponds to a rejection rate of about 40%.

The articles in this Research Topic may be grouped into four thematic groups: autoimmune blistering diseases, cutaneous drug reactions and allergies, rare genetic diseases and miscellaneous reports.

Autoimmune blistering dermatoses

This thematic group comprises seven articles that focus on cases of blistering dermatoses with unusual manifestations or associations with other diseases. Each article presents a unique case that sheds light on the clinical presentation, diagnosis, and treatment of these conditions.

For instance, Quattri et al. (a) [Corrigendum: Quattri et al. (b)], report on a 74-year-old woman with anti-laminin 332 mucous membrane pemphigoid (MMP) and severe pharyngolaryngeal involvement, who was successfully treated with topical and systemic therapy but later developed respiratory distress and required a tracheotomy.

Moro, Mariotti et al. describe a case of a 68-year-old woman with multiple sclerosis and scleroderma who developed bullous pemphigoid, and suggest that autoimmune diseases affecting the skin or organs where BP180 and BP230 are present could trigger the onset of bullous pemphigoid.

Moro, Ciccone et al. report on a second case: a 50-year-old man developed erosive lesions on the skin, oral mucosae and genital mucosae after Imiquimod treatment for superficial basal cell carcinoma. Diagnosis of pemphigus vulgaris was confirmed by immunofluorescence. Treatment with prednisolone led to complete remission in 4 weeks. Imiquimod therapy may induce pemphigus vulgaris in some patients. Sequential treatment should be considered for patients with multiple and large basal cell carcinoma to reduce the risk of adverse events.

In another article, Schauer et al. report on a male patient with a minimal manifestation of mucous membrane pemphigoid who presented with recurrent erosions in the urethral outlet area and gingiva, and who was diagnosed after a latency of around 4 years.

Kita et al. describe a case of a 15-year-old Japanese male who was initially suspected to have autoimmune bullous disease. However, the patient was ultimately diagnosed with prurigo pigmentosa and treated successfully with oral doxycycline hydrochloride hydrate and topical tacrolimus ointment. This case highlights that prurigo pigmentosa can mimick autoimmune blistering dermatoses including clinical, histological and immunologic aspects. This shows that the detection of autoantibodies does not necessarily imply their pathogenicity - and that all findings must be taken into account in order to come to a diagnosis.

The article by Didona et al. reports on a young patient with Behçet's disease who showed IgG autoantibodies against BP180, with the most common autoantigen in bullous pemphigoid, without developing blisters or urticarial-like plaques.

Finally, Minakawa et al. report on a case of a 20-year-old woman with autoimmune bullous disease (AIBD) who experienced mucocutaneous lesions after receiving the COVID-19 mRNA vaccine. The patient had IgG and IgM autoantibodies against epidermal basement membrane zone (BMZ) and a history of epidermolysis bullosa acquisita (EBA). Treatment with prednisolone resolved the lesions. The authors suggest that clinicians should be aware of the potential development of bullous pemphigoid-like AIBDs after COVID-19 mRNA vaccination.

Cutaneous drug reactions and allergies

This topic covers 4 cases of toxic epidermal necrolysis and unusual forms of fixed drug eruption, as well as a case of LTP syndrome, which is relatively rare in Northern Europe in the described form.

The case reported by Paulmann et al. highlights the challenges of distinguishing two rare skin diseases, generalized bullous fixed drug eruption (GBFDE) and toxic epidermal necrolysis (TEN), and elucidates the importance of a distinct clinical presentation and detailed medication history. The patient, a 42-year-old male, presented with more than 50% skin detachment without defined areas of exanthema or erythema and a history of one prior event of TEN caused by acetaminophen, allopurinol or amoxicillin one and a half years before. The histology of a skin biopsy was unable to distinguish between the two diseases. The course of the disease, the later clinical presentation, and the medical and medication history, however, were in favor of a diagnosis of GBFDE. Metamizol was later on identified as the culprid drug because the patient developed a relapse after he received an additional dose of this medication.

Lin et al. describes a severe case of vanishing bile duct syndrome, a rare drug-induced disease characterized by cholestasis and ensuing ductopenia, in a patient who presented with concurrent Stevens-Johnson syndrome and hemophagocytic lymphohistiocytosis after the ingestion of non-steroidal anti-inflammatory drugs. Despite improvement in vanishing bile duct syndrome with steroid treatment, the patient died due to hypovolemic shock combined with septic shock episodes.

Zang et al. describe a rare case of TEN in a hepatitis A virus infection with acute-on-chronic liver failure patient. The patient's condition progressively worsened with a severe generalized rash, bullae and epidermal detachment accompanied by severe erosive mucosal lesions. The intravenous infusion of corticosteroids alleviated the patient's hypersensitivity, and the patient obtained lasting remission without severe adverse reactions and complications.

Otsuka et al. present the first case of a severe non-pigmenting fixed drug eruption (NPFDE) exhibiting general symptoms caused by chondroitin sulfate sodium. The patient of this case was a 44-year-old man who developed a severe rash and fever after taking chondroitin sulfate sodium. The rash was initially limited to the thighs but later spread to other parts of the body, and the patient developed systemic symptoms such as fever and arthralgia. The diagnosis of NPFDE was confirmed by skin biopsy showing infiltration of CD8-positive T-cells.

Albert et al. describe a rare case of a woman in Northern Europe who had an anaphylactic reaction to a meal containing various foods, including fruits, nuts, oats, wheat, and salmon. Allergy tests showed that the woman was not sensitized to Bet v1, which is common in birch food syndrome. Instead, she had a non-specific lipid transfer protein (nsLTP)-mediated food allergy, which is becoming increasingly common in Northern Europe.

The authors suggest that LTPs should be considered as potential allergens, particularly for patients who experience severe reactions after consuming LTP-containing foods.

Rare genetic diseases

Rare diseases clearly show the limits that are still faced by modern medicine (3). In the following articles, the authors describe how they faced this challenge of rare diseases and how they coped with it.

Costa et al. describe a case of a 30-year-old male patient, who underwent excision/grafting procedures for a giant congenital melanocytic nevus (CMN) at a child, and was diagnosed with metastatic melanoma more than 20 years later. The case highlights the importance of lifetime monitoring with once-yearly dermatological examination for large/giant CMN patients and the need for further clinical trials evaluating novel therapies for NRAS-mutant melanoma.

Hereditary angioedema with normal C1 inhibitor and unknown mutation (HAE-nC1INH-UNK), an exceedingly rare subtype of HAE, appears to be often misdiagnosed in patients who actually have mast cell-mediated angioedema. The article by Buttgereit et al. presents criteria for diagnosing HAE-nC1INH and emphasizes the importance of ruling out common differential diagnoses to reduce patients' disease burden and healthcare costs.

VEXAS syndrome is an autoinflammatory disease associated with severe inflammatory symptoms in adults. It is caused by somatic mutations in the UBA1 gene, leading to various clinical manifestations such as recurrent fever, skin conditions, vasculitis, and organ inflammation. A case study of a 64-year-old man with VEXAS syndrome presented by Tozaki et al. shows that treatment with oral prednisone and tocilizumab resulted in the resolution of symptoms. The study also measured derivatives of reactive oxygen metabolites (d-ROMs) as an indicator of oxidative stress and found that d-ROM levels decreased significantly after treatment.

Xue et al. report on a case of generalized pustular psoriasis (GPP) successfully treated with secukinumab, a monoclonal antibody that targets interleukin-17A. GPP is a rare and severe form of psoriasis that presents with erythematous, aseptic pustules, and common systemic symptoms include fever and myalgia.

Miscellaneous reports

This thematic group comprises five unique cases describe unusual diseases, new diagnostic methods and new therapeutic options.

Scholl et al. describe a patient with long-term plaque psoriasis and psoriasis arthropathica who was treated with methotrexate and adalimumab. Then, this patient developed cutaneous pseudolymphoma caused by Leishmania infantum infection. Discontinuation of the anti-TNF-treatment resulted in resolution of the infection without anti-leishmanial therapy, highlighting the critical role of TNF in parasite control.

Yu Y. et al. describe a case of a 15-year-old boy with perifolliculitis capitis abscedens et suffodiens (PCAS), who was successfully treated with adalimumab and baricitinib, as the initial treatment of adalimumab and oral isotretinoin was insufficient. The proposed regimen is reported to be non-invasive and safe for treating PCAS.

Nie et al. report on a case of a 41-year-old Chinese woman who developed yellow-brown plaques in her eyebrows for several months following a tattoo in the same area. She was diagnosed with eyebrow tattoo-associated sarcoidosis, which was treated with topical corticosteroids with little effect. The treatment was a watch-and-wait strategy, including the recommendation to avoid permanent makeup.

Ha-Wissel et al. use optical coherence tomography (OCT) to monitor the individual treatment response of four patients with psoriasis or atopic dermatitis to biologic agents. Imaging parameters, such as epidermal thickness and vascular density, were used to enable objective quantification of inflammation in psoriasis or atopic dermatitis in selected representative skin areas. OCT potentially serves as an instrument to monitor biologic therapy in inflammatory skin diseases.

Yu Q. et al. applied chemical nail avulsion as a treatment for a 25-year-old male patient with onychomycosis. The conventional method proved to be effective in treating the patient, suggesting that chemical nail avulsion might be a viable alternative for the treatment of onychomycosis.

Concluding remarks

The Research Topic "*Case Reports in Dermatology*" offers a collection of 21 insightful articles that shed light on the challenges of contemporary medicine. These case reports emphasize the importance of precise diagnosis and effective treatment, often demanding a multidisciplinary strategy. Beyond the insights gleaned from these textual and visual accounts, it's vital to recognize the inherent value of tactile and three-dimensional impressions in the educational journey of budding dermatologists. Engaging with real-world tactile experiences equips them with a comprehensive understanding, ensuring a holistic approach to dermatology. By assimilating knowledge from these cases and blending it with hands-on experiences, dermatologists can broaden their expertise, ultimately enhancing the quality of patient care.

Author contributions

AR: Conceptualization, Writing—original draft, Writing—review and editing. TH: Conceptualization, Writing—original draft, Writing—review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 25 August 2022
DOI 10.3389/fmed.2022.991918

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 12 July 2022
ACCEPTED 11 August 2022
PUBLISHED 25 August 2022

CITATION
Yu Q, Wang Y, Yang H, Li W and Yang L (2022) Case report: Novel use of the conventional method- chemical nail avulsion may be effective for treatment of green nail syndrome. *Front. Med.* 9:991918. doi: 10.3389/fmed.2022.991918

Case report: Novel use of the conventional method- chemical nail avulsion may be effective for treatment of green nail syndrome

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Green nail syndrome (GNS) is a triad of green discoloration of the nail plate, proximal paronychia, and distal onycholysis. *Pseudomonas aeruginosa* is known to be the most common causative agent; however, there is no unified standard for the diagnosis and treatment of GNS. Thus, treatment is challenging and often refractory. Here, we report three representative cases with different predisposing factors, including trauma-related, occupation-related, and onychosis-related GNS. Patients with GNS accompanied by onycholysis were instructed to undergo chemical nail avulsion combined with topical antibiotics, and favorable curative effects were observed in all cases. Chemical nail avulsion with urea powder as a conventional method may be an effective treatment for GNS and warrants clinical generalization.

KEYWORDS

green nail syndrome, *Pseudomonas aeruginosa*, predisposing factors, chemical nail avulsion, urea powder

Introduction

Green nail syndrome (GNS), also known as chloronychia, is an infectious disorder characterized by a greenish discoloration of the nail plate (1) most commonly caused by *Pseudomonas aeruginosa* (2). Although ubiquitous in nature, *P. aeruginosa* is unable to colonize dry environments and rarely affects healthy skin (3).

Green nail syndrome has a chronic course and often affects aesthetics. However, to date, there is no unified standard for its diagnosis and treatment. Thus, treatment of GNS is always challenging and often refractory (4). Safer, more effective, and widely applicable treatments are urgently needed. Previous studies have reported various predisposing factors to the condition such as trauma, occupation, onychomycosis (5), and psoriasis

(6). It is important to carefully analyze the predisposing factors of GNS to assist in the treatment of patients.

Although GNS has rarely been reported in the literature, it is not uncommon in clinical practice. In our hospital, an average of 200 patients with onychosis seek medical advice per week, among those patients about 1–2 patients with GNS. Herein, we describe three representative cases of GNS accompanied by onycholysis, with different predisposing factors. The patients were treated with chemical nail avulsion, and favorable curative effects were achieved.

Case description

Case 1

A 25-year-old woman presented with an asymptomatic partial color change of the left thumbnail, which she noticed immediately after the removal of gel nail polish. The patient had a history of obtaining regular manicures and denied a history of trauma or the nail's prolonged exposure to moisture.

Physical examination revealed green discoloration of the middle to distal parts of the left thumbnail, accompanied by a slight distal onycholysis (**Figure 1A**). Direct mycologic examination of scrapings and culture was negative, however, the bacterial culture of the nail scraping was positive for *P. aeruginosa*. A drug susceptibility test with *P. aeruginosa* showed its sensitivity to levofloxacin. The patient was then instructed to remove the gel nail polish and cease manicures. She received chemical nail avulsion with urea powder for 3 days to remove the left distal portions of the thumbnail plate, and subsequently applied topical nadifloxacin twice daily. At 3-month follow-up, the nail discoloration had resolved completely (**Figure 1B**).

Case 2

A 36-year-old otherwise healthy man was referred to our hospital in the summer with a 2-month history of green discoloration on his right third fingernail. Discoloration appeared at the distal margin and gradually spread throughout the nail; a similar nail lesion involved the thumbnail. The patient was regularly engaged in garbage sorting and wore gloves daily for extended periods of time.

Dermatologic examination showed dark-greenish pigmentation and onycholysis on the right third fingernail (**Figures 2A,C,D**), green discoloration adjacent to the lateral nail fold on the right thumbnail, and corresponding periungual skin red swelling (**Figures 2A,B**). Fungal coinfections were excluded by direct fluorescence microscopy and culture. However, bacterial cultures of nail scrapings were positive for *P. aeruginosa*. An *in vitro* drug susceptibility test indicated high sensitivity to levofloxacin. The patient was instructed to stop wearing gloves and keep his hands dry. He was then treated with chemical nail avulsion combined with nadifloxacin, as in Case 1. The nail plates were cured after 6 months of follow-up (**Figures 2E–G**).

Case 3

A 57-year-old woman developed an asymptomatic black-greenish discoloration in both thumbnails over the preceding 5 months. The thumbnail plates had gradually appeared yellowish and thickened, and full discoloration had begun 1 month prior to presentation to our hospital. The patient had no significant medical history, had not received any medication, and had not experienced any previous fingernail injuries. As someone with domestic duties, her hands were constantly exposed to water, detergents, and soaps.

Clinical examination of the patient's thumbnails revealed thickened nail plates with green discoloration from the distal edge to the middle nail plates, as well as onycholysis at the site of the discolored area (**Figure 3A**). Direct mycological examination of nail scrapings showed positivity for fungal hyphae, and cultures were identified as *Trichophyton rubrum*. The bacterial culture was positive for *P. aeruginosa*. A drug susceptibility test showed levofloxacin sensitivity. The patient was instructed to keep the hands dry and treat the primary onychosis. She received treatment with systemic oral itraconazole 400 mg/day for 7 days per month for 3 months along with topical chemical nail avulsion and nadifloxacin. At 2-month follow-up, the nail discoloration had faded significantly. The nail plates had completely healed at 5-month telephone follow-up (**Figure 3B**).

Discussion

Green nail syndrome is a triad of green discoloration of the nail plate, proximal paronychia, and distal onycholysis. The characteristic greenish discoloration of the nail results from the antibiotic pigments pyoverdine and pyocyanin produced by *P. aeruginosa*. This bacterium is an opportunistic human pathogen that can cause a wide variety of skin diseases, including GNS, interdigital infection, hot tub folliculitis, and ecthyma gangrenosum (3). Generally, characteristic clinical findings are sufficient for diagnosis of GNS; however, it must be differentiated from onychomycosis caused by dematiaceous fungi, yellow nail syndrome, subungual hematoma, subungual melanoma, exogenous pigmentation, medication-induced effects, and glomus tumor (7). Pathogenic identification, pathological

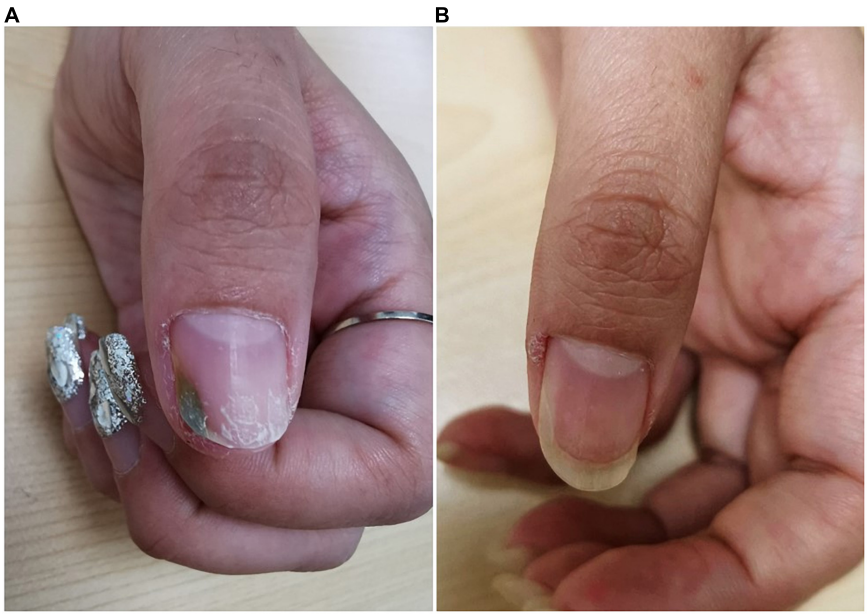

FIGURE 1
Clinical image of Case 1. **(A)** Nail plate of a patient with trauma-related GNS at initial visit. **(B)** Subsided lesions at 3 months following topical antibiotic treatment.

examination, and dermoscopic patterns can be used to confirm intractable GNS.

The pathogenesis of GNS has not been fully elucidated in the literature. However, it is known that when the nail plates undergo barrier impairment or prolonged exposure to a moist environment, *P. aeruginosa* infection is more likely (4). The potential predisposing factors suggested in this study were as follows.

(1) Trauma-related GNS: The predisposing factors for this type of GNS are mainly nail trauma including manicures, wearing tight shoes, and biting or picking nails (8). Nail trauma disrupts the integumentary barrier, making the nail conducive to *P. aeruginosa* invasion. In case 1, the patient obtained regular manicures that involved the cutting, filing, and shaping of the nails; pushing back of cuticles, and application of gel polish onto the nails. These procedures can cause nail plate trauma, enable *P. aeruginosa* colonization, and subsequently create an occlusive environment by covering the nail with gel nail polish, resulting in infection by this pathogen.
(2) Occupation-related GNS: GNS can be viewed as an occupationally triggered disease in those with domestic duties, cleaners, barbers, dishwashers, bakers, and medical personnel (9). These patients usually have a history of long duration of exposure to water or moist conditions and deny a history of nail trauma or previous onychosis. In this report, the patient in Case 2 engaged in garbage sorting and wore gloves for lengthy periods daily, causing hyperhidrosis leading to a moist environment, which is an ideal condition for the growth of *P. aeruginosa*.
(3) Onychosis-related GNS: This type often occurs in patients with prior nail problems, such as onychomycosis, onycholysis, chronic paronychia, and psoriasis. A recent study demonstrated that GNS was identified concurrently with onycholysis in 87% of individuals (10), among which onychomycosis was the most prevalent concomitant disease. Fungal infections create tunnel-like structures in nail keratin, and *P. aeruginosa* can proliferate in these spaces. In Case 3, the patient's previous onychomycosis contributed to the entry of *P. aeruginosa*; additionally, as someone with domestic duties, her hands often had prolonged exposure to water. These two factors led to the occurrence of GNS.

An optimal treatment regimen for GNS has not yet been established. Topical or systemic antibiotics may be used to eradicate infections, with the application of topical antibiotics showing increased effectiveness in patients due to economic convenience, convenient administration, and few adverse reactions. However, in this drug delivery method, antibiotics may not fully permeate the nail plate to reach the infected area. Removal of the involved nail can massively reduce pathogen load, promote drug permeation, and accelerate disease recovery (11). Currently, chemical nail avulsion with high-concentration urea has gradually superseded surgical avulsion

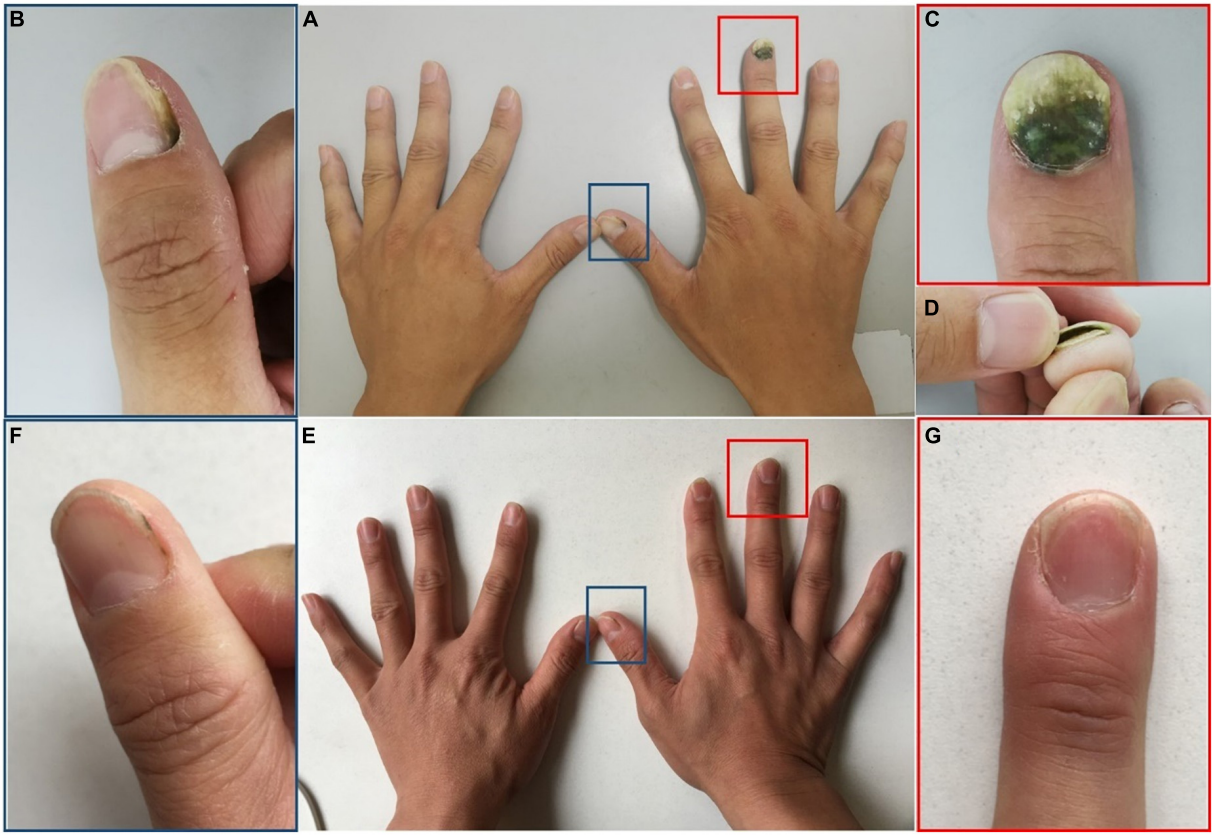

FIGURE 2
Clinical image of Case 2. **(A–D)** Nail plate of a patient with occupation-related GNS at initial visit. **(E,F)** Subsided lesions at 6 months following chemical nail avulsion combined with topical antibiotic treatment. **(B,C)** Are partial magnifications of **(A)**. **(D)** Is profile image of **(C)**. **(F,G)** Are partial magnifications of **(E)**.

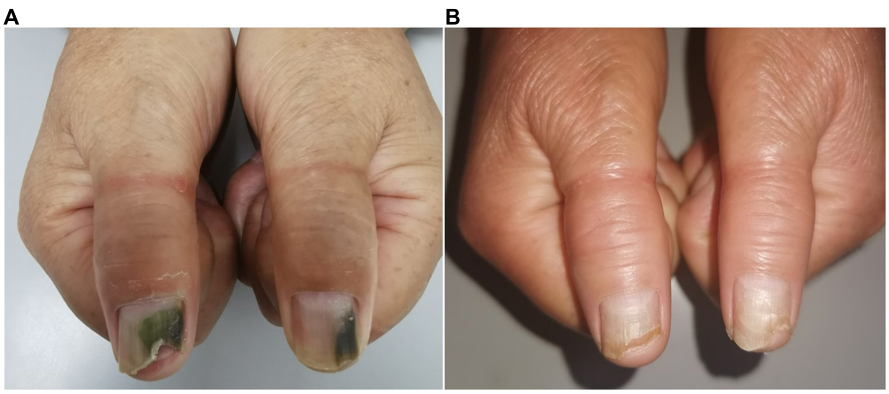

FIGURE 3
Clinical image of Case 3. **(A)** Nail plate of a patient with onychosis-related GNS at initial visit. **(B)** Improved lesions at 2 months following chemical nail avulsion combined with topical antibiotic treatment.

owing to levels of minimal to no pain, low risk of infection, and no risk of hemorrhage. Urea, a keratolytic agent, can disrupt the cell/cell adhesion of corneocytes in the nail plate, and a high concentration can soften the nail plate for easy removal of the infected area without damage to the matrix and nail bed (12, 13). Chemical nail avulsion using urea

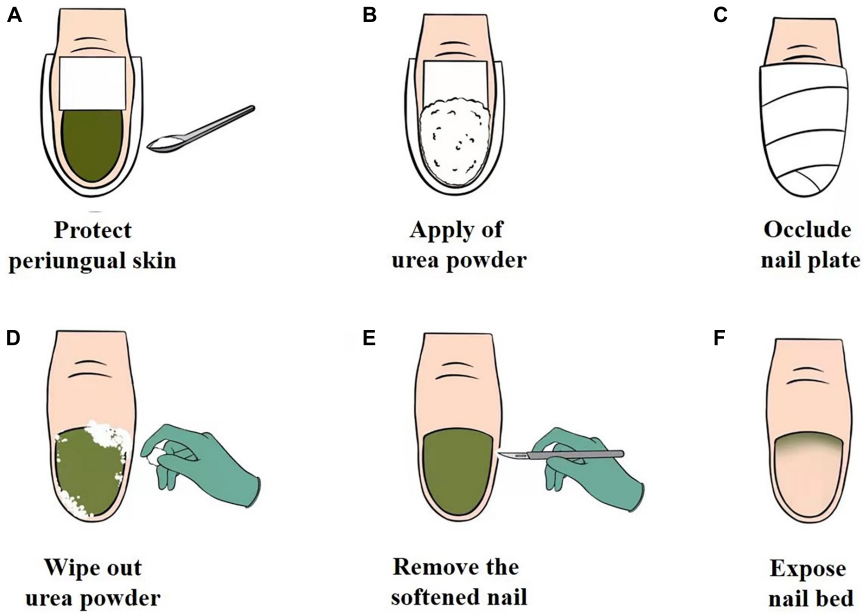

FIGURE 4
(A–F) The operational chemical nail avulsion procedure using urea powder. **(A)** Protection of the periungual skin of the affected nail plate with waterproof plaster. **(B)** Application of urea powder to the affected nail plate. **(C)** Occlusion of the affected nail plate with waterproof plaster. **(D)** Removal of urea powder with an alcohol cotton ball. **(E)** Removal of the softened nail. **(F)** Exposure of the nail bed.

powder (100% urea without any other ingredients), as a conventional method, has been widely used in the treatment of onychomycosis with a definite therapeutic effect for many years in our hospital (14). Therefore, we assessed this as a treatment for patients with GNS.

The procedure for chemical nail avulsion with urea powder is shown in Figure 4. The periungual area was protected with a waterproof plaster to prevent chemical irritation of the soft tissue (Figure 4A), followed by the application of urea powder (Figure 4B); and then occluded with a waterproof plaster (Figure 4C). The patient was guided to keep the nail occluded and to avoid wetting the treated area. If the patient were to wet the treated area during chemical nail avulsion, this can lead to urea dissolution. Dissolved urea may then permeate into periungual skin of the treated area and cause skin maceration, slight irritation, or reduction in the efficiency of nail plate removal. After 3–5 days of occlusion, the waterproof plaster was removed, the nail was cleansed with 75% wipes (Figure 4D), and the softened nail was removed using a scalpel (Figures 4E,F). Following this, the patient was instructed to administer topical antibiotics. This approach was able to break the moist, occlusive environment to keep the nail dry and prevent *P. aeruginosa* persistence. This treatment approach softens the infected area of nail plate to achieve its complete removal in an average of 3–5 days, with minimal known adverse reactions. Chemical nail avulsion with urea powder can be applied to all patients, including the elderly and children, as all procedures are performed by podiatry in a hospital setting. In this report, patients who were diagnosed with GNS with concomitant onycholysis underwent chemical nail avulsion combined with topical antibiotics and acquired excellent therapeutic effects. Further studies are required to confirm the efficacy, safety, and tolerability of this treatment.

In conclusion, GNS is a distinct clinical condition that often occurs in patients with various predisposing factors that favor the growth of *P. aeruginosa*. Chemical nail avulsion with urea powder may be an effective method for the treatment of GNS and deserves to be clinically generalized.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Dermatology Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QY and YW: design and drafting of the work, analysis, acquisition, and interpretation of data. HY: laboratory testing and data analysis. WL and LY: study design, revision, and finalization of the manuscript. All authors have contributed to the manuscript and approved the submitted version.

Funding

This work was supported by the Science and Technology Commission of Shanghai Municipality (grant number 20Y11905600) and Shanghai Municipal Commission of Health and Family Planning (grant number 20194Y0337).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 15 September 2022
DOI 10.3389/fmed.2022.1000954

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 22 July 2022
ACCEPTED 29 August 2022
PUBLISHED 15 September 2022

CITATION
Quattri E, Zussino M, Lauro W, Berti E, Marzano AV and Genovese G (2022) Case report: A case of anti-laminin 332 mucous membrane pemphigoid associated with severe pharyngolaryngeal involvement. *Front. Med.* 9:1000954. doi: 10.3389/fmed.2022.1000954

Case report: A case of anti-laminin 332 mucous membrane pemphigoid associated with severe pharyngolaryngeal involvement

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A 74-year-old woman presented with a 30-day history of blisters and erosions in the oral cavity, trunk, and left eye conjunctival mucosa, also reporting a weight loss of 15 kg in the last 3 months. Histopathological examination showed subepidermal blisters and lymphocytic infiltrates with rare eosinophils in the superficial dermis. Direct immunofluorescence showed linear deposits of IgG and C3 along the dermal-epidermal junction and salt-split skin indirect immunofluorescence confirmed the presence of linear deposits of IgG along the blister floor. Indirect immunofluorescence revealed antibodies against laminin 332 using recombinant laminin 332 expressed in human HEK293 cells, and commercial ELISA kits (Euroimmun, Padova, Italy) did not reveal antibodies against BP230 and BP180 antigens. Anti-laminin 332 mucous membrane pemphigoid (MMP), a condition often associated with a hidden neoplasm, was diagnosed. In our case, the paraneoplastic nature of MMP was excluded. Thus, topical treatment with triamcinolone acetonide 0.1% in orabase once daily for 30 days, oral prednisone 0.75 mg/kg/day and rituximab were started to relieve symptoms. Conjunctival, nasal and oral erosions improved, as well as skin lesions, but later the patient was tracheotomized due to respiratory distress linked to the appearance of pharyngolaryngeal synechiae.

KEYWORDS

laminin 332, mucous membrane pemphigoid, pharyngolaryngeal involvement, paraneoplastic, epiligrin, laminin 5

Introduction

Mucous membrane pemphigoid (MMP) encompasses a heterogeneous group of subepithelial autoimmune blistering diseases mediated by autoantibodies against different adhesion molecules of the epithelial basement membrane zone (BMZ) such as BP180, BP230, collagen VII, integrin α6β4 and laminin 332 (1, 2). It predominantly affects the mucous membranes and is characterized by linear deposition of IgG, IgA or C3 along the epithelial basement membrane (1, 2). The diagnosis is confirmed by histology

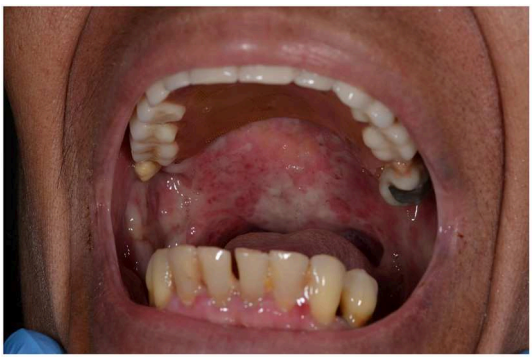

FIGURE 1
Blisters and erosions in the oral cavity of our patient.

and direct and indirect immunofluorescence techniques; more expensive techniques such as laminin-332 transfected cell technique are more rarely performed (3). In MMP patients with anti-laminin 332 autoantibodies, an increased risk for neoplasms associated with a poor prognosis – especially within the 1st year from MMP onset – has been described (4–6). Egan et al. (4) reported in these patients a relative risk for cancer of 6.8, similar to that of adults with dermatomyositis. Consistent with these data, some authors regarded anti-laminin 332 MMP as a paraneoplastic syndrome triggered by an autoimmune response to laminin 332 expressed in the tumor cells and in the normal mucosal tissue. (7) Furthermore, some case reports pointed out a clinical remission of anti-laminin 332 MMP after treatment of the associated neoplasm (8–10). More recently, however, three independent studies did not confirm the association between anti-laminin 332 autoantibodies and cancer in their cohort of patients (11–13). Significant correlations between serum levels of anti-laminin 332 antibodies and disease activity have been shown by means of ELISA, (14) immunoblotting and IIF (6) and in a recent meta-analysis of 200 published MMP cases an association of anti-laminin 332 antibodies with pharyngo-laryngeal and oro-pharyngo-laryngeal (15) involvements has been found.

Herein, we describe a case of anti-laminin 332 MMP with severe pharyngolaryngeal involvement which was not associated with neoplasms.

Case description

A 74-year-old woman presented with a 30-day history of blisters and erosions in the oral cavity, trunk, and left eye conjunctival mucosa. Even if her medical history was unremarkable, the patient reported a weight loss of 15 kg in the last 3 months. She denied recent intake of new drugs. Dermatological examination revealed erosions in the aforementioned areas and in the nasal mucosa (Figure 1). Eye examination confirmed synechiae in both eyes, while the otolaryngological evaluation excluded the presence of pharyngolaryngeal synechiae. Differential diagnoses included pemphigus *versus* MMP. Histopathological examination showed subepidermal blisters and lymphocytic infiltrates with rare eosinophils in the superficial dermis (Figure 2A). Direct immunofluorescence showed linear deposits of IgG and C3 along the dermal-epidermal junction, while indirect immunofluorescence confirmed the presence of linear deposition of IgG along the basement membrane (Figure 2B). Commercial ELISA kits (Euroimmun, Padova, Italy) did not reveal antibodies against BP230 and BP180 antigens. Indirect immunofluorescence on salt split skin confirmed the linear IgG deposition along the blister floor (Figure 2C). We demonstrated the presence of anti-laminin 332 antibodies in the patient's serum using a sensitive and highly specific indirect IF test using recombinant laminin 332 expressed in human HEK293 cells, with all laminin subunits α3, β3, and γ2 (Figure 2D), as already performed in other studies (6, 12, 16). We made a diagnosis of anti-laminin 332 MMP and requested in-depth blood chemistry and instrumental examinations due to the suspicion of a hidden neoplasm. In the meantime, the patient was given topical treatment with triamcinolone acetonide 0.1% in orabase once daily for 30 days and oral prednisone 0.75 mg/kg/day to relieve symptoms. Lymph node and abdomen ultrasound, mammography and total body computed tomography were oncologically negative. Paraneoplastic MMP was ruled out, so the patient was started on infusion therapy with rituximab. Conjunctival, nasal and oral erosions rapidly improved as well as skin lesions. Only mild itching persisted. At the time of diagnosis, Mucous Membrane Pemphigoid Disease Area Index score (MMPDAI) was 44 points, reduced to 15 during follow-up. However, 6 months after rituximab treatment the patient was tracheotomized for acute respiratory failure due to pharyngolaryngeal synechiae, a difficult-to-prevent outcome in MMP.

Discussion

In the last decade, there has been mounting body of evidence that patients' subsets identified by the binding of their serum autoantibodies to specific target antigens may have different disease phenotypes, clinical outcomes and association with malignancy. In particular, retrospective studies have highlighted an increased risk for cancer in anti-laminin 332 MMP. Laminin 332, formerly called epiligrin or laminin 5, is a major component of the BMZ and consists of three subunits (α3, β3, and γ2). It is localized at the interface between lamina lucida and lamina densa and contributes to anchoring hemidesmosomal structures such as BP180 and integrin α6β4 to collagen VII. (17) Antibodies against laminin 332 are reported in 12 up

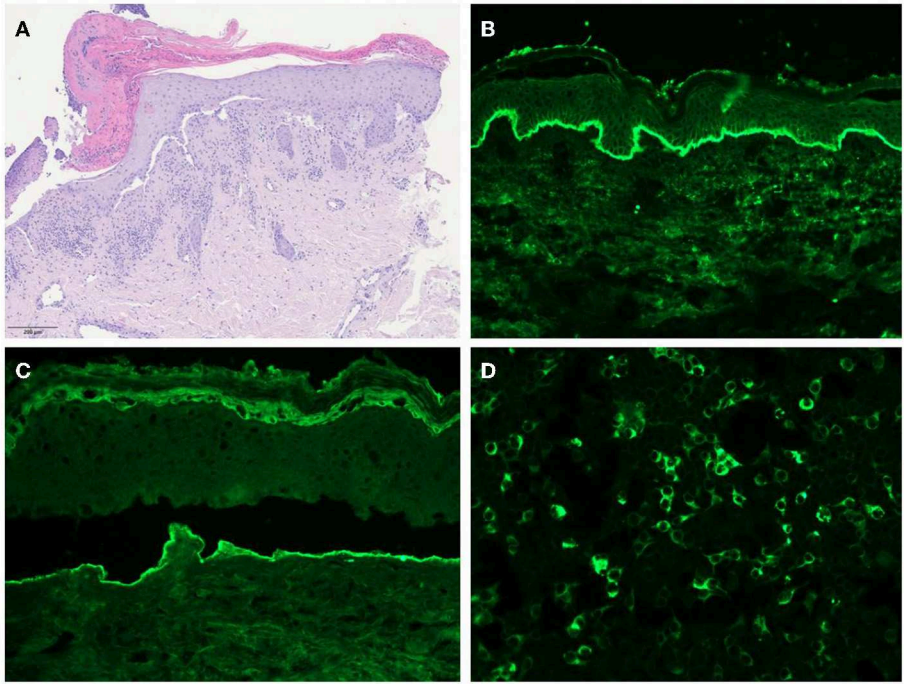

FIGURE 2
(A) Histology showing subepidermal blisters and lymphocytic infiltrates with rare eosinophils in the superficial dermis. **(B)** Direct immunofluorescence revealing IgG deposits along the dermal-epithelial junction. **(C)** Salt-split skin indirect immunofluorescence showing IgG deposits along the floor of the blister. **(D)** Indirect immunofluorescence test using recombinant laminin 332 expressed in human HEK293 cells revealing the presence of anti-laminin 332 antibodies in the patient's serum.

to 75% of MMP patients (11, 12, 18–21). The pathogenicity of anti-laminin 332 antibodies has been demonstrated by the passive transfer of IgG against laminin 332 into neonatal and adult mice (21, 22). The pathogenic mechanisms explaining the differences in terms of cancer risk between patients with anti-laminin 332 MMP and anti-integrin α6β4 MMP are still a matter of speculation. Laminin 332 is expressed in the extracellular matrix of different neoplasms and its levels may be over- or under-represented based on the tumor type. (19) Laminin 332 has been proposed to act as an oncosuppressor molecule, whose increased cleavage by means of tumor-associated proteases may promote cancer progression. (20) Thus, anti-laminin 332 antibodies can be hypothesized to determine *in vivo* alterations mimicking the action of these proteases by inhibiting laminin 332 or activating tumor-associated proteases (21). However, in the light of *in vitro* inhibiting properties on tumor growth of anti-laminin 332 antibodies (11), it can also be postulated that anti-laminin 332 antibody production may be due to a paraneoplastic autoimmune response toward common molecules shared by the tumor and adhesion structures of the BMZ.

However, in contrast with the retrospective studies that have highlighted an increased risk for cancer in anti-laminin 332 MMP, more recent studies failed to confirm the association between anti-laminin 332 MMP and cancer (11–13). In our case, accurate instrumental investigations apparently rule out any hidden neoplasm. On the other hand, in line with literature data showing an association of anti-laminin 332 antibodies with severe pharyngo-laryngeal and oro-pharyngo-laryngeal involvements (15), our patient developed acute respiratory failure due to pharyngolaryngeal stenosis. In conclusion, potential complications linked to high morbidity and/or mortality, such as esophageal/laryngeal stenosis, are relatively frequent in anti-laminin 332 MMP and require a prompt diagnosis and an effective treatment in order to delay or halt the disease progression.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

EQ and GG wrote the paper. MZ and WL contributed in drafting the manuscript. EB performed laboratory tests. AM

critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was partially funded by Italian Ministry of Health, Current research IRCCS.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TYPE Correction
PUBLISHED 15 December 2022
DOI 10.3389/fmed.2022.1100467

OPEN ACCESS

APPROVED BY
Frontiers Editorial Office,
Frontiers Media SA, Switzerland

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 16 November 2022
ACCEPTED 06 December 2022
PUBLISHED 15 December 2022

CITATION
Quattri E, Zussino M, Lauro W, Berti E, Marzano AV and Genovese G (2022) Corrigendum: Case report: A case of anti-laminin 332 mucous membrane pemphigoid associated with severe pharyngolaryngeal involvement. *Front. Med.* 9:1100467. doi: 10.3389/fmed.2022.1100467

Corrigendum: Case report: A case of anti-laminin 332 mucous membrane pemphigoid associated with severe pharyngolaryngeal involvement

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KEYWORDS

laminin 332, mucous membrane pemphigoid, pharyngolaryngeal involvement, paraneoplastic, epiligrin, laminin 5

A corrigendum on
Case report: A case of anti-laminin 332 mucous membrane pemphigoid associated with severe pharyngolaryngeal involvement

by Quattri, E., Zussino, M., Lauro, W., Berti, E., Marzano, A. V., and Genovese, G. (2022). *Front. Med.* 9:1000954. doi: 10.3389/fmed.2022.1000954

In the published article, there was an error in the **Funding** statement. [There was no funding statement]. The correct **Funding** statement appears below.

Funding

This study was partially funded by Italian Ministry of Health, Current research IRCCS.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 23 September 2022
DOI 10.3389/fmed.2022.964062

OPEN ACCESS

EDITED BY
Andreas Recke,
University of Lübeck, Germany

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 12 July 2022
ACCEPTED 29 August 2022
PUBLISHED 23 September 2022

CITATION
Zang X, Chen S, Zhang L and Zhai Y (2022) Toxic epidermal necrolysis in hepatitis A infection with acute-on-chronic liver failure: Case report and literature review. *Front. Med.* 9:964062. doi: 10.3389/fmed.2022.964062

Toxic epidermal necrolysis in hepatitis A infection with acute-on-chronic liver failure: Case report and literature review

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Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are acute inflammatory skin adverse reactions characterized by epidermal exfoliation and multi-site mucositis and are considered medical emergencies. The risk factors for SJS/TEN include immune disorders, malignancy, and genetic susceptibility. In most cases, medication is considered to be the leading cause of TEN. In addition, several studies suggest that infections, such as the herpes simplex virus, human immunodeficiency virus (HIV), *Mycoplasma pneumoniae*, streptococcus, and meningococcus infections, can trigger the occurrence of SJS/TEN. In this rare case, we share our experience managing TEN in a hepatitis A virus infection with an acute-on-chronic liver failure patient. A 38-year-old man was infected with hepatitis A virus on the basis of liver cirrhosis and progressed to acute-on-chronic liver failure. As the infection progressed, the target-like skin lesions accompanied by mucosal involvement worsened. The condition of the patient progressively worsened with a severe generalized rash, bullae, and epidermal detachment accompanied by severe erosive mucosal lesions. His skin detachment area gradually involved 30% of the body surface area (BSA), and the disease progressed to TEN. The intravenous infusion of corticosteroids alleviated the patient's hypersensitivity, and the patient obtained lasting remission without severe adverse reactions and complications.

KEYWORDS

toxic epidermal necrolysis, acute-on-chronic liver failure, hepatitis A virus, liver cirrhosis, case report

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, severe skin adverse reactions characterized by epidermal loss and multisite mucositis, accompanied by systemic disturbance (1). Both have the same risk factors and causes, which can be distinguished based on the proportion of the affected body surface area (BSA). Among them, patients with an epidermal detachment of <10% of BSA are diagnosed with SJS. Detachment of the epidermis of 10–30% of BSA is diagnosed with the overlapping group of SJS/TEN, whereas the involvement of more than 30% of BSA

is diagnosed with TEN. It is reported that the incidence of SJS/TEN is about 1–3 cases per million per year (2). Although rare, the average mortality rate for SJS is <10%, and the mortality rate for TEN is more than 30%. The mortality rate is even higher in patients with sepsis, elderly patients, and patients with a sizeable epidermal detachment area at admission (3). In most cases, medication is considered to be the leading cause of TEN (4). In addition, several studies have proven that viruses, mycoplasma, and bacterial infections are all triggers of SJS/TEN, and the etiology of a few cases is still unclear.

This study reports a case of TEN caused by hepatitis A virus infection with acute-on-chronic liver failure. To our knowledge, this is the first case report to discuss TEN in acute-on-chronic liver failure secondary to acute hepatitis A infection.

Case presentation

In June 2019, a 38-year-old male patient presented to a local hospital due to fatigue, loss of appetite, jaundice, skin pruritus, and a recent weight loss of about 7 kg. The patient denied a history of chronic diseases and relevant infectious diseases. The abdominal CT showed liver cirrhosis, splenomegaly, and varicose veins. The laboratory tests found that the hepatitis A virus antibody IgM was positive, and the total bilirubin was 392.5 μmol/L. The alanine aminotransferase was 390 U/L, and the aspartate aminotransferase was 198 U/L. He was given hepatoprotective therapy with a coenzyme complex. The coenzyme complex was a compound preparation that mainly contained coenzyme A, coenzyme I [nicotinamide adenine dinucleotide (NAD)], and reduced glutathione (GSH), but the patient's liver function did not significantly alleviate. Hematochezia occurred after 3 days, and the bleeding was reduced after hemostatic treatment with aminocaproic acid and octreotide. After 15 days, rashes appeared on the whole body, accompanied by fever with a maximum temperature of 39.0°C, and he was then transferred to our hospital for further treatment on 27 June. The timeline of the clinical events and treatment strategies is shown in Figure 1.

At the time of admission, the patient was lethargic, with a heart rate of 90 beats/min, a respiratory rate of 18 breaths/min, and hypotension of 97/56 mmHg. In addition, he had severe jaundice, icteric sclera, and liver palms. There were densely distributed congested maculopapular rashes on the trunk; however, the skin between the rashes was normal. The routine blood test results showed decreases in white blood cell count (1.31×10^9/L), hemoglobin count (99 g/L), red blood cell count (3.04×10^{12}/L), and platelet count (61×10^9/L). As for blood biochemical parameters, the laboratory found an increase in alanine aminotransferase (65 U/L), aspartate aminotransferase (84 U/L), total bilirubin (372.8 μmol/L), conjugated bilirubin (281.2 umol/L), prothrombin time (17.50 s), and international-normalized-ratio (INR, 1.6), as well as a decrease in total protein (45.3 g/L), and albumin (24.6 g/L). He was diagnosed with decompensated liver cirrhosis, acute hepatitis A, and lower gastrointestinal bleeding (Figure 2). As the liver function worsened, according to the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) (5), the disease progressed to acute-on-chronic liver failure. Meanwhile, the patient denied ever having had a skin rash before and had no family history of the condition as well. He received supportive treatment with fluid supplementation, skin care, and regular infection screening. The skin was regularly flushed with sterile water, but the rash did not alleviate significantly.

On 7 July, his symptoms showed a clinical deterioration. He developed a new congestive maculopapular rash on the inner sides of both upper arms and both sides of the armpits, with severe involvement of the palms of the hands and soles of the feet. In addition, the diffuse congestive rash was seen mainly on the trunk, accompanied by itching (Figure 3A). The patient was treated with methylprednisolone (40 mg, bid) combined with intravenous immunoglobulin (IVIG, 10 g/day) in a separate intensive care unit.

On 12 July, the patient complained of a new rash that gradually worsened, and the rash was more severe in the areas of pressure (buttocks and back), on which a positive Nikolsky sign can be induced by mechanical pressure on the skin. Blisters first appeared on the hands, feet, and lips and gradually spread to the limbs, shoulders, and neck (Figure 3C). The blisters ulcerated on their own, accompanied by pain and a burning sensation. Meanwhile, the oropharyngeal mucosa was swollen, and the patient had difficulty opening the mouth and swallowing due to repeated bleeding and crusting. Moreover, the oral mucosa and external genitalia could be seen ulcerated and exuded. The patient's condition further worsened, the skin detachment area gradually involved 30% of the BSA, and the disease further progressed to TEN. On 15 July, the patient complained of dryness in both eyes and a foreign body sensation in the blinking eyes. The ophthalmologist's examination revealed bilateral conjunctival congestion and edema, yellow sclera, and corneal transparency. The patient was diagnosed with conjunctivitis and was given levofloxacin eye drops as an anti-inflammatory treatment. In addition, daily eye care was performed to clear inflammatory secretions. On July 16, the patient received a high intravenous dose of methylprednisolone (50 mg, bid) and IVIG (400 mg/kg/day). However, the patient did not alleviate significantly. Since the therapeutic effect of intravenous methylprednisolone and IVIG was not obvious, starting from 19 July, the patient received an intravenous injection of hydrocortisone (200 mg, bid). After 5 days, there was no further necrosis and exfoliation of the skin rash and no new lesions (Figures 3D,E). Meanwhile, there was no obvious increase in external genital mucosal erosion and skin breakdown in the buttocks, and the pain was slightly reduced. Due to the massive exfoliation of the patient's epidermis, levofloxacin was added to prevent skin infections. Lyophilized Recombinant Human Acidic Fibroblast Growth Factor (rhaFGF) was used with infrared physiotherapy to promote wound healing, and

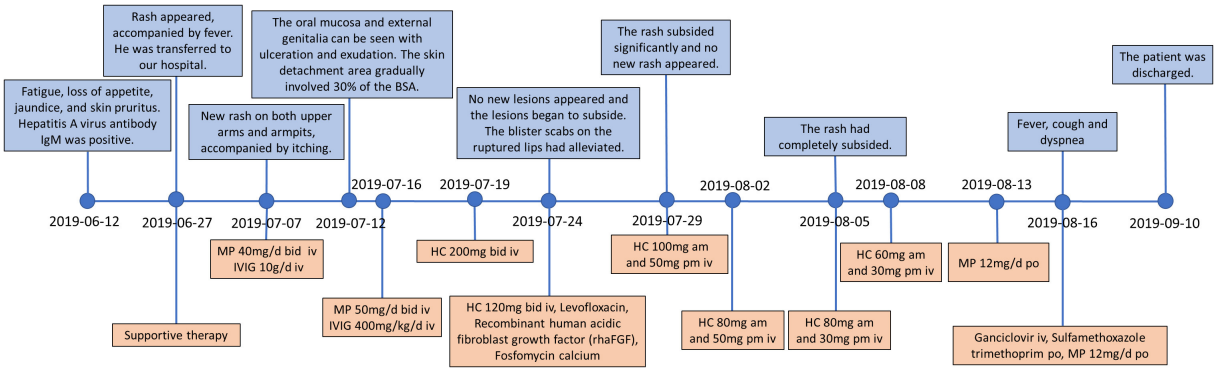

FIGURE 1
Timeline of the clinical events and treatment strategies. MP, methylprednisolone; HC, hydrocortisone; IVIG, intravenous immunoglobulin.

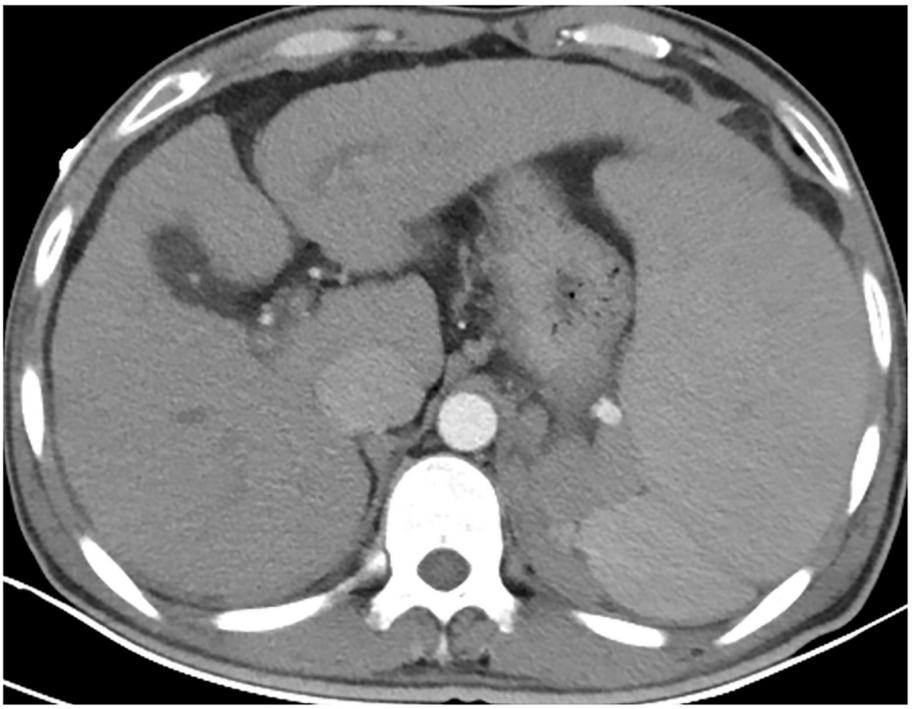

FIGURE 2
Contrast-enhanced CT of the whole abdomen revealed liver cirrhosis, splenomegaly, ascites, and portal hypertension. Varicose veins in the lower part of the esophagus. Varicose veins around the fundus of the stomach and around the spleen (2 July).

fosfomycin calcium was used to prevent wound infection. Considering that the disease was under control, hydrocortisone has been applied in sufficient quantities for 5 days, and the dosage was reduced with the aim of transitioning to oral administration and eventually discontinuation. On 31 July, the rash on the face and neck completely subsided. The blisters and erosions of the external genital mucosa were obviously improved. The ophthalmologist's examination showed mild scleral yellowing and pale conjunctiva without congestion or edema. The conjunctivitis was improved and no ocular sequelae appeared. On 5 August, the patient's rash completely subsided. On 13 August, the intravenous infusion of hydrocortisone was stopped and transitioned to oral methylprednisolone tablets. The progression of the patient's skin lesions was shown in Figure 3.

On 16 August, the patient had a sudden fever, cough, and dyspnea. The body temperature rose to 37.6°C. The white blood cell count was 6.9 × 10^9/L; the percentage of

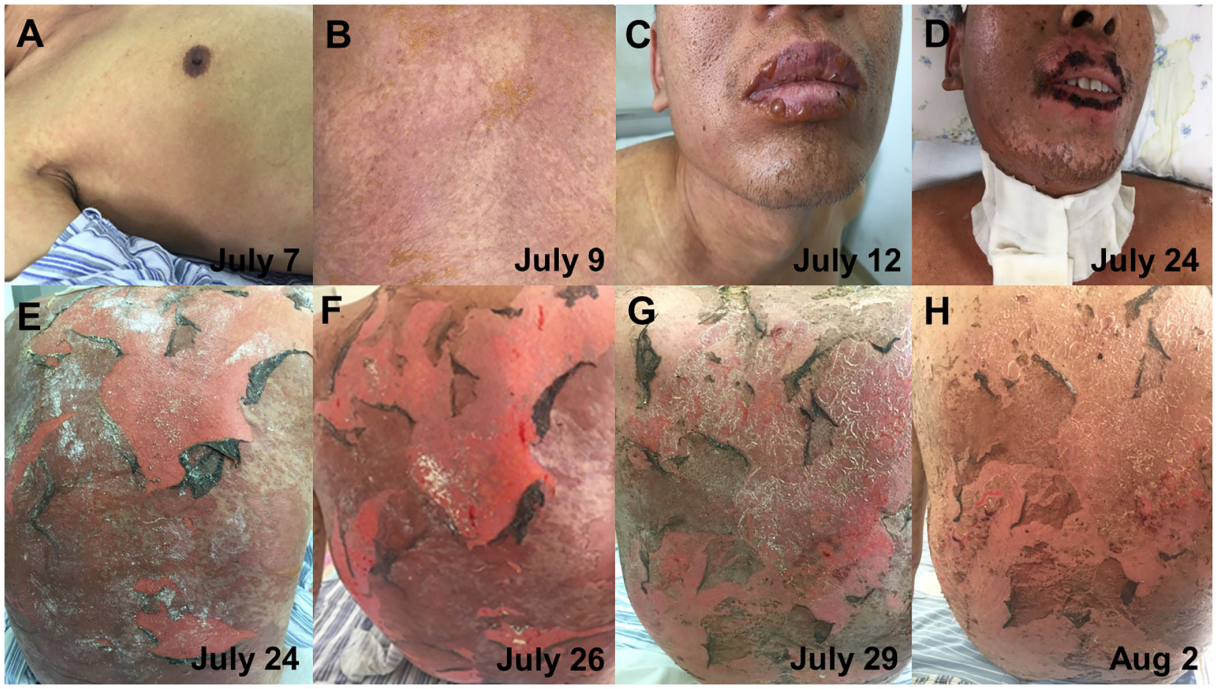

FIGURE 3
The progression of skin lesions. **(A)** The patient developed a new congestive maculopapular rash, mainly on the trunk (7 July). **(B)** The patient has a dense rash on the back (9 July). **(C)** Blisters appeared on the lips (12 July). **(D)** The scab on the lips had improved (24 July). **(E,F)** Diffuse erythema and epidermal detachment on the back (24 and 26 July). **(G,H)** The detachment of the epidermis on the back gradually improved (29 July and 2 August).

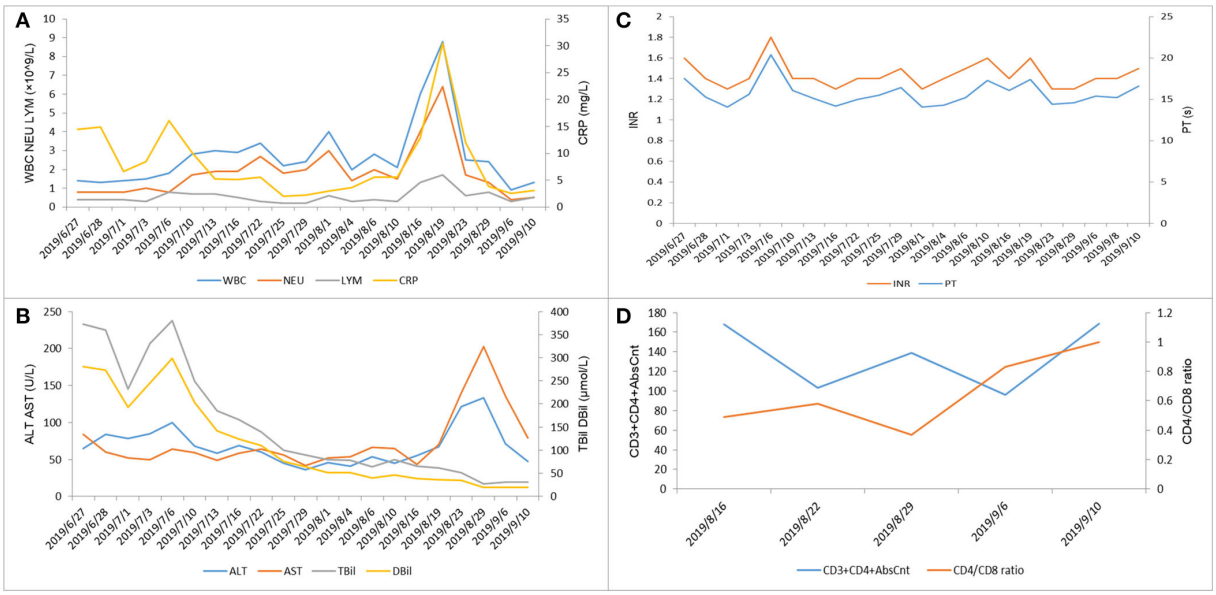

FIGURE 4
Laboratory test indicators during the hospitalization of this patient. **(A)** White blood cells ($\times 10^9$/L), neutrophils ($\times 10^9$/L), lymphocytes ($\times 10^9$/L), and C-reactive protein (mg/L). **(B)** Alanine aminotransferase (U/L), aspartate aminotransferase (U/L), total bilirubin (μmol/L), and direct bilirubin (μmol/L). **(C)** International normalized ratio (INR) and prothrombin time (s). **(D)** CD3+CD4+AbsCnt and CD4/CD8 ratio.

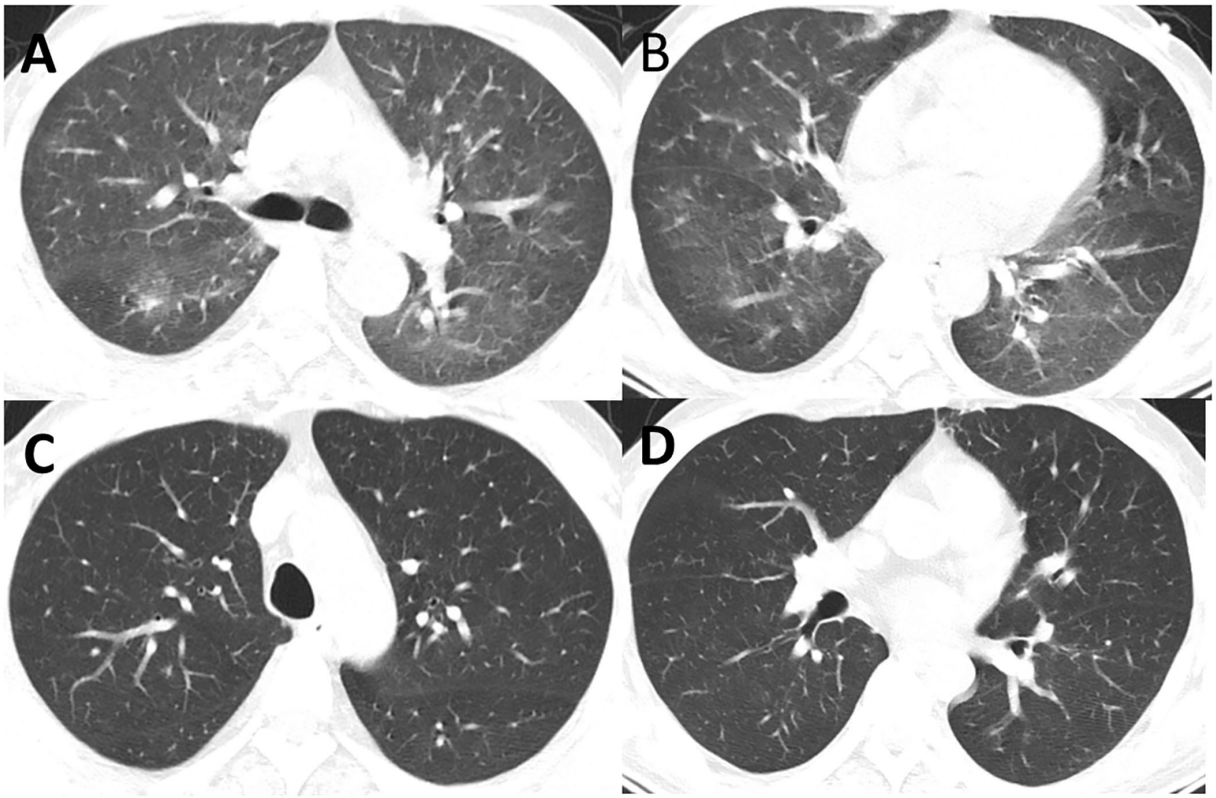

FIGURE 5
(A,B) CT showed new inflammation and inflammatory nodules in the lingual segment of the right lung and the upper lobe of the left lung (16 August). **(C,D)** CT showed that the double pneumonia was less than before (5 September).

neutrophils was 65.8%, C-reactive protein was 19.4 mg/L, and the absolute count of CD4+ T cells was <200 (Figure 4D). The antibodies for Cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae, and Chlamydia pneumoniae were all negative. The chest CT showed ground glass-like and grid-like changes (Figure 5). Considering that the patient's weakened immune system may cause opportunistic infections, the possibility of Pneumocystis carinii infection was high. He was given an oral antibiotic sulfamethoxazole-trimethoprim, ganciclovir intravenously, combined with oral methylprednisolone tablets 12 mg/day. The cough and fever improved after the medications, and the patient's inflammation indicators gradually decreased. Furthermore, the chest CT confirmed the improved pulmonary infection. We instructed the patient to reduce methylprednisolone tablets to 2 mg/day every week until discontinuation. Important indicators were regularly reviewed throughout the treatment process (Figure 4).

After the treatment mentioned above, the patient's rash completely subsided and the function indexes of multiple organs tended to stabilize and improve before being discharged from the hospital on 10 September. After 2 months, the patient was admitted for follow-up on 5 November. As for the blood biochemical parameters, the laboratory found an increase in alanine aminotransferase (91 U/L), aspartate aminotransferase (151 U/L), total bilirubin (97.1 umol/L), conjugated bilirubin (79.3 umol/L), as well as a decrease in albumin (24.4 g/L). Meanwhile, his skin lesions had completely subsided, with no recurrence or complications and no ocular sequelae appeared.

Discussion and literature review

Medication is considered to be the leading cause of SJS/TEN. A number of studies have also proven that infections, such as herpes simplex virus and human immunodeficiency virus (HIV), are all triggering factors for SJS/TEN (4). Since the first case of TEN caused by hepatitis A virus was reported in Israel in 1989 (6), there have been no other studies demonstrating the association between hepatitis A virus and subsequent TEN. Here, we report a case of TEN in acute-on-chronic liver failure secondary to hepatitis A. In this study, the patient was treated with hepatoprotective drugs and hemostatic medications before the rash onset, none of which were reported as suspicious high-risk pathogenic drugs in the literature. In addition, we

assessed causality between these drug exposures and TEN using the Algorithm of Drug Causality in Epidermal Necrolysis (ALDEN) score (7). Based on the ALDEN score, the coenzyme complex with an ALDEN score of 1 point was classified as an unlikely cause. With an ALDEN score of −1 point, aminocaproic acid and octreotide were classified as very unlikely causes. Meanwhile, the laboratory tests have demonstrated that the patient was not infected with other pathogenic bacteria or viruses. Therefore, we believe that the patient's TEN was presumably caused by the hepatitis A virus. We will discuss our findings in terms of the following three sections, namely the pathogenesis, treatment, and infection monitoring of SJS/TEN.

Pathogenesis of SJS/TEN

The pathogenesis of SJS/TEN is not yet fully understood, but T cell-mediated drug-specific cytotoxicity, genetic linkage, granulysin, and other mechanisms are considered to play a crucial role in the pathogenesis of SJS/TEN. The histopathological study of SJS/TEN skin lesions showed that the diffuse apoptosis of keratinocytes caused the patient's extensive epidermal detachment (8). Studies have analyzed the live immune cells in the vesicular fluid of patients with TEN and found that T lymphocytes are the primary cell type. In the early stage of the disease, cytotoxic T lymphocytes (CTL) are the most critical cells in the blister fluid (9, 10). Therefore, the occurrence of TEN may be a T cell-mediated cytotoxic reaction against keratinocytes, which leads to the apoptosis of keratinocytes. Medication is considered to be the leading cause of TEN. The drug antigen activates T cells through the interaction of T cell receptor (TCR) and MHC on antigen presenting cells, leading to the clonal expansion of CD8+ CTL. Cytotoxic T cells can induce extensive apoptosis of TEN epidermal cells through the perforin/granzyme B pathway (11). In addition, the granulysin secreted by drug-specific CTL cells and NK cells is also a key mediator of keratinocyte apoptosis in SJS/TEN (12).

Several previous studies have identified infections associated with SJS/TEN, such as the herpes simplex virus, human immunodeficiency virus (HIV), and *Mycoplasma pneumoniae*, which can trigger the occurrence of SJS/TEN. For example, the occurrence of SJS/TEN in patients with HIV is thought to be the result of multiple synergistic factors. The incidence of skin adverse reactions in patients with HIV was inversely correlated with the peripheral blood CD4+ T cell count and CD4+/CD8+ ratio in a study cohort (13). Another study suggested that HIV infection predisposed skin to TEN *via* depletion of skin-directed CD4+ T cells. Furthermore, an imbalance in the CD4+/CD8+ cell ratio may predispose the development of TEN (14). In our case, the patient was infected with hepatitis. A virus on the basis of liver cirrhosis. With the further deterioration of liver function, he developed acute-on-chronic liver failure. Patients with acute-on-chronic liver failure often show an attenuated activity of immune cells (15). In addition, our patient showed a decrease in peripheral blood CD4+ T cell count and a CD4+/CD8+ cell ratio. On the basis of current evidence, it is undeniable that infections play an important role in the formation of SJS/TEN (4). However, the pathogenesis and pathogenic mechanisms of infection leading to SJS/TEN still need further research.

Patients with SJS/TEN usually have extensive and varying degrees of mucosal involvement, especially in the eyes. Studies have shown that more than half of patients with SJS/TEN are accompanied by severe ocular complications (SOCs) (16). The acute phase is often accompanied by a variety of manifestations, such as eyelid edema, conjunctival edema or congestion, conjunctivitis, keratitis, or corneal ulceration. In the chronic stage, it manifests as severe sequelae, such as dry eye, trichiasis, and vision loss (17). It is worth noting that the pathogenesis and genetic background appear to be different in SJS/TEN patients with and without SOCs. For example, among patients with drug-related SJS/TEN, patients with SJS/TEN caused by the use of acetaminophen for the common cold showed a higher incidence of SOCs than those patients with SJS/TEN caused by the use of other drugs (18). In addition, there were racial differences in HLA types associated with SJS/TEN and SOCs. For example, HLA-A*02:06 is associated with Japanese and Korean patients, while HLA-B*44:03 is associated with Japanese, Indian, and European ancestry Brazilian patients (4, 17, 19).

In addition to cold medications, infections, such as viruses or mycoplasma, may play a triggering role in the onset of SJS/TEN with SOCs (20). In this case of toxic epidermal necrolysis caused by hepatitis A virus, the patient was diagnosed with conjunctivitis. Conjunctivitis has improved and the ocular signs and symptoms have completely subsided after the above treatment without serious ocular sequelae. Cold medicines are considered to be one of the most common factors causing SJS/TEN with SOCs. A retrospective study from Japan showed that the patient's age and the cold medicine used as the exposure drug were predictors of increased ocular severity in the acute phase. Meanwhile, the incidence of severe chronic ocular sequelae increased with the severity of the eye in the acute phase (21). In our case, however, the patient presented with relatively mild ocular symptoms and no serious sequelae developed, which could be related to hepatitis A virus infection. There are fewer studies on viral infections leading to SJS/TEN with SOCs at present, and further studies on the severity of SJS/TENS with SOCs and ocular management are needed to reduce the occurrence of serious ocular sequelae.

Treatment of SJS/TEN

At present, there is no specific treatment for SJS/TEN that has shown effectiveness in clinical trials. Previous studies have shown that several common treatments include supportive therapy, immunosuppressive drug therapy, intravenous

immunoglobulin, and plasma exchange (22). Among them, the use of methylprednisolone pulse therapy and intravenous immunoglobulin combined with methylprednisolone pulse therapy is increasing for severe and rapidly progressive cases. The effectiveness of these two treatments is still controversial. A study from India demonstrated that low-dose immunoglobulin combined with steroid therapy showed benefits in reducing mortality and preventing disease progression (23). However, another retrospective study involving 281 patients found that compared with supportive treatment, intravenous immunoglobulin and steroids had no significant effect on patient mortality (24).

Studies have shown that if high-dose glucocorticoids are given to patients with liver failure, it may increase the incidence of adverse events (25). In our case, the patient was diagnosed with acute-on-chronic liver failure after admission, and the rash was not yet typical. Therefore, the patient was given supportive treatment based on the principle of safety. Unfortunately, the rash worsened on the 10th day of admission, and the patient received an intravenous infusion of methylprednisolone (40 mg, bid) in combination with IVIG (10 g/day). Although there is no conclusive evidence that any interventions are more effective than conservative treatments, a recent case report found that as the patient's disease worsened, a gradual escalation of treatment protocol helped the patient recover from the disease (26). When the treatment is effective, the patient's skin lesions and erythema usually begin to recover within 3 days after starting the treatment (27). However, in our case, the therapeutic effect of this treatment was not obvious. In a retrospective study, the authors found that the steroid pulse therapy of two patients who died was started more than 7 days after the onset of the disease. It is speculated that the delay of treatment may weaken the effect of steroid pulse therapy (27). In another case of TEN caused by the use of amphetamine, the author believed that the delayed use of intravenous immunoglobulin may have caused the delay of the patient's re-epithelialization (28). These results suggest that early interventions may be effective and contribute to the improved prognosis of SJS/TEN. However, steroid pulse therapy does remain controversial at present, and large-scale randomized clinical trials are needed to find out the effectiveness, exact timing, and optimal dose of steroid therapy for SJS/TEN.

Liver injury is one of the common complications of SJS/TEN. Studies have shown that liver disease history is a risk factor for poor prognosis of SJS/TEN patients with liver injury (29). In our case, with the further deterioration of liver function and rash, the patient's condition worsened and the treatment became more difficult. Even worse, the patient's immune system was weak, which increased the possibility of causing sepsis. Considering that known inflammation and pro-apoptotic mechanisms play a role in SJS/TEN, there is no consensus on the selection of steroid hormones and the optimal dosage. We hypothesize that the role of steroid hormones in the clinical treatment of patients with sepsis gives us some thoughts. Studies have shown that high-dose or long-term use of methylprednisolone is not beneficial in the treatment of sepsis and may increase the incidence of adverse events (30). However, the use of low-dose hydrocortisone (<400 mg/day) will shorten the reversal time of shock, and the incidence of complications caused by steroids is relatively low (31, 32). This may be because methylprednisolone has a stronger immunosuppressive effect, while hydrocortisone has more mineralocorticoid effects and vasoactive properties. As the effect of intravenous infusion of methylprednisolone combined with immunoglobulin therapy was not obvious, after fully considering the patient's condition, the treatment was changed to intravenous hydrocortisone infusion (200 mg, bid). With the gradual improvement of the rash, the dosage of hydrocortisone was reduced to the oral dose and finally withdrawn completely.

In addition, previous case reports described the effectiveness of intravenous hydrocortisone in the treatment of SJS/TEN. In a case report from the United States, a small dose of hydrocortisone combined with vitamin C and thiamine (HAT therapy) was used to treat a patient with SJS/TEN overlap. The patient's condition was significantly improved within 48 h (33). In another case report from the United Kingdom, when the disease progressed, effectiveness was shown after the gradual escalation of the treatment protocol from oral prednisolone to intravenous hydrocortisone (26). For steroid therapy, the choice of hormones, the appropriate dosage, the ideal treatment time, and safety still need to be further explored in clinical research.

Importance of infection monitoring

In our study, the patient developed a lung infection on 16 August, and the absolute value of CD4+ T cell count was <200. Considering that the patient's weakened immune system may cause opportunistic infections. Due to the extensive detachment of the epidermis, mucosal damage, and drug-induced immunosuppression, patients with SJS/TEN are prone to infectious complications (34), and the high mortality rate of SJS/TEN is mainly due to the occurrence of sepsis (35). In addition, studies have shown that the use of corticosteroids may increase the infection rate and mortality of patients with SJS/TEN (36). Unfortunately, our patient had acute-on-chronic liver failure. Patients with liver failure are susceptible to bacterial and fungal infections due to the immune paralysis of circulating immune cells (15). Therefore, we believe that infection monitoring is necessary for patients with SJS/TEN, especially those with underlying diseases that easily lead to low immunity or who are treated with corticosteroids. It is still controversial whether the use of corticosteroids for the treatment of SJS/TEN will bring serious negative effects on patients. Previous studies have shown that the early use of corticosteroid pulse therapy can significantly reduce the occurrence of ocular complications, and it has no significant

effect on mortality and the incidence of sepsis (24, 37). Whether steroid therapy treatment of SJS/TEN will produce serious negative effects still needs further research.

Over the recent decades, we have gained a deep understanding of the immunological mechanism of SJS/TEN. With the progress in drug research, there are several reports on SJS/TEN caused by new drugs and new biological products. For instance, several cases of SJS/TEN due to COVID-19 vaccination have been reported recently, and this poses new challenges for the early diagnosis and identification of pathogenic factors of SJS/TEN (38, 39). At the same time, infection and autoimmune diseases are also potential pathogenic factors. The possible interaction between infection and drugs or the interaction between different drugs needs further study. The mortality of SJS/TEN is usually high, and its treatment is very complicated and difficult. There is currently no consensus and universally applicable treatment plan. Most studies are published in the form of case reports, systematic reviews, and meta-analyses. More large-scale randomized clinical trials are needed to formulate individualized treatment plans based on the different pathogenic factors of patients and the severity of the disease.

This study has some limitations. Unfortunately, the patient developed abnormal coagulation due to acute-on-chronic liver failure; therefore, we were unable to perform a histological examination. There is a need for further research which would provide more insight into the mechanisms and early recognition of TEN induced by the hepatitis A virus.

Conclusion

In our study, we report a case of TEN caused by hepatitis A virus infection with acute-on-chronic liver failure. In addition, we explored the treatment of TEN in combination with acute-on-chronic liver failure for the first time, including the dose of hormones and the duration of therapy. The potential occurrence of serious cutaneous adverse events requires medical staff to be aware of such skin reactions when managing patients with the hepatitis A virus. Meanwhile, we emphasize the importance of early clinical suspicion, infection monitoring, and management by a multidisciplinary team.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

This study protocol meets the requirements of the Medical Ethics Committee of Shengjing Hospital of China Medical University. The patient provided his written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

YZ contributed to the conception and design of this study and finally approved the manuscript version to be submitted. XZ and SC analyzed the data and wrote the manuscript. LZ contributed to clinical management of the patient and constructive discussions and revised the manuscript as well. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank the patient and his family for consenting to publish this case report.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 27 September 2022
DOI 10.3389/fmed.2022.995883

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 16 July 2022
ACCEPTED 12 September 2022
PUBLISHED 27 September 2022

CITATION
Ha-Wissel L, Yasak H, Huber R, Zillikens D, Ludwig RJ, Thaçi D and Hundt JE (2022) Case report: Optical coherence tomography for monitoring biologic therapy in psoriasis and atopic dermatitis.
Front. Med. 9:995883.
doi: 10.3389/fmed.2022.995883

Case report: Optical coherence tomography for monitoring biologic therapy in psoriasis and atopic dermatitis

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Biologic therapies are increasingly used to treat chronic inflammatory skin diseases such as psoriasis and atopic dermatitis. In clinical practice, scores based on evaluation of objective and subjective symptoms are used to assess disease severity, leading to evaluation of treatment goals with clinical decisions on treatment initiation, switch to another treatment modality or to discontinue current treatment. However, this visual-based scoring is relatively subjective and inaccurate due to inter- and intraobserver reliability. Optical coherence tomography (OCT) is a fast, high-resolution, *in vivo* imaging modality that enables the visualization of skin structure and vasculature. We evaluated the use of OCT for quantification and monitoring of skin inflammation to improve objective assessment of disease activity in patients with psoriasis and atopic dermatitis. We assessed the following imaging parameters including epidermal thickness, vascular density, plexus depth, vessel diameter, and vessel count. A total of four patients with psoriasis or atopic dermatitis were treated with biologic agents according to current treatment guidelines. OCT was used to monitor their individual treatment response in a target lesion representing disease activity for 52 weeks. Psoriatic and eczema lesions exhibited higher epidermal thickness, increased vascular density, and higher vessel count compared to uninvolved skin. An upward shift of the superficial vascular plexus accompanied by smaller vessel diameters was seen in psoriasis in contrast to atopic dermatitis, where larger vessels were observed. A response to biologic therapy was characterized by normalization of the imaging parameters in the target lesions in comparison to uninvolved skin during the observation period of 52 weeks. Optical coherence tomography potentially serves as an instrument to monitor biologic therapy in inflammatory skin diseases. Imaging parameters may enable objective

quantification of inflammation in psoriasis or atopic dermatitis in selected representative skin areas. OCT may reveal persistent subclinical inflammation in atopic dermatitis beyond clinical remission.

KEYWORDS

optical coherence tomography (OCT), skin inflammation, psoriasis, atopic dermatitis, biologic therapy, *in vivo* imaging

Introduction

Psoriasis and atopic dermatitis are both common inflammatory skin diseases. About 30% of the patients with psoriasis (1) and about 10% with atopic dermatitis (2) require a systemic therapy due to their disease severity. Due to their safety profile and efficacy, biologic agents (3–5), and small molecules (6) are being increasingly used. A main drawback of these innovative treatments is that they may lose efficacy over time and that not all patients respond to a selected therapy. Also, in some cases the current dosing is not needed and potentially exposes the individuals to adverse events that may be avoided by adjusted dosing that fits their individual needs. Currently, however, indication and continuation of treatment are mainly dependent on clinical scores. These clinical scores are based on visual examination that might be biased by the experience of the clinician resulting in inter- and intraobserver variabilities (7, 8).

Facing these limitations, we aimed to develop an objective and more reliable evaluation method using image-based scoring to enable objective guidance of clinical decision making to avoid delayed and inconsistent therapy decisions.

Optical coherence tomography (OCT) is a fast, high-resolution, *in vivo* imaging method with growing influence in the dermatological practice, especially in non-melanoma skin cancer (9–12). The imaging technique of OCT is based on Michelson interferometry (13). In the assessment of inflammatory skin diseases, additional information on vascular network is of special interest. OCT angiography based on speckle variance detection allows the visualization of cutaneous vasculature (14). It was reported that different vascular patterns and shapes (dots, blobs, coils, lines, curves, and serpiginous vessels) could distinguish healthy skin from lesional inflammatory skin (15, 16). In psoriatic skin, structural changes and alterations in vessel density and size were shown (17–19). Previous studies demonstrated the correlation between histopathological findings and structural features of psoriasis and chronic inflammation apparent in OCT (20, 21). In atopic dermatitis, epidermal hypertrophy and vascular depth were discussed as important parameters for disease severity (22).

In the past 20 years, OCT was used for single time-point observations and short-term monitoring of psoriasis and atopic dermatitis (23–25). Based on these observations, here, we performed an interim analysis of a large ongoing prospective, long-term, observational study using a clinically approved OCT system for monitoring patients with psoriasis and atopic dermatitis undergoing biologic treatment over 52 weeks.

Materials and methods

Subjects and biologic therapies

The study was conducted according to the guidelines of the Declaration of Helsinki and ethical approval was obtained from the Ethics Committee of the University of Lübeck. Adult subjects eligible for inclusion were diagnosed with moderate to severe plaque psoriasis or atopic dermatitis and received treatment according to current treatment guidelines. Written informed consent was obtained from all patients. OCT data of three patients with psoriasis and one patient with atopic dermatitis was analyzed. They underwent biologic treatment with anti-IL-17 ixekizumab (n = 1), anti-IL-23 risankizumab (n = 1), anti-TNF-α certolizumab (n = 1) or anti-IL-4Rα dupilumab (n = 1). At baseline, week 2, 4, 16, 28, 40, and 52 of treatment, clinical scores were determined and OCT scans were performed at one lesional site and one perilesional control site for each patient (**Figure 1**).

Clinical scoring

Visual-based scores such as psoriasis area and severity index (PASI) (7), eczema area and severity index (EASI) (8), and body surface area (BSA) (7) were determined by an experienced physician. Additional digital dermoscopy images were captured with DermoGenius ultra polarized (DermoScan GmbH, Regensburg, Germany).

To date, whole body OCT scanners do not exist and large-area scanning cannot be performed within a reasonable time. Thus, we must select target lesions for small-area imaging. The total sign score (TSS) was used to evaluate selected skin areas. For psoriasis, three clinical signs including erythema, induration, and desquamation were assessed using a 5-point scale (0 absent, 1 mild, 2 moderate, 3 severe, and 4 very severe)

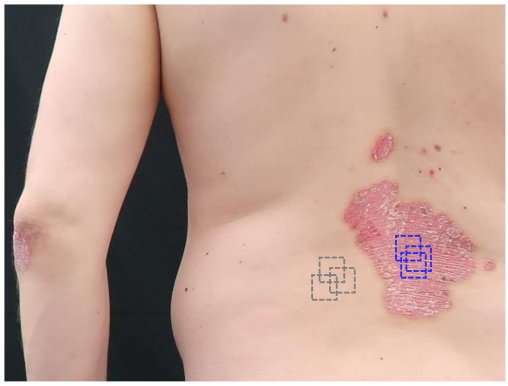

FIGURE 1
Selection of target lesions and control sites for optical coherence tomography (OCT). Patient 3 was a 45-year-old male patient with plaque psoriasis showing PASI = 10.8 and BSA = 10% at baseline. A representative target lesion (blue) on his trunk was selected for 52 weeks monitoring. A perilesional location was selected as the control site (gray). The scans were performed repetitively at the same lesional and non-lesional location.

with a total range of 0–12 (26). For atopic dermatitis, six clinical signs including erythema, edema/papulation, oozing/crusting, excoriation, lichenification, and dryness were graded using a 4-point scale (0 absent, 1 mild, 2 moderate, and 3 severe) with a total range of 0–18 (27).

Optical coherence tomography

We utilized a clinically approved VivoSight Dx OCT scanner (Michelson Diagnostics, Maidstone, Kent, UK). The emission wavelength is 1,305 nm. The lateral and axial resolution is <7.5 μm and <5 μm, respectively. The scan area is 6 mm × 6 mm. The penetration depth is about 1.2 mm. A three-dimensional image stack with 6 mm width records a sequence of 180 B-scans with an interslice spacing of 33.3 μm. Images were acquired as vertical B-scans and *en-face* scans. The acquisition time of an image stack is about 30 s generating both structural and vascular images. The *en-face* scans are reconstructed images to show skin layers at a constant depth from the skin surface. For an image stack with 1.2 mm depth, a sequence of 120 *en-face* scans with an interslice spacing of 10 μm can be obtained. Patients were at rest prior to scanning. Measurement conditions (location, patient position, and room temperature) were kept constant. Three regions of the same target lesion and three regions of its perilesional, clinically uninvolved skin area as reference were repetitively imaged. The target lesion was located either in upper extremities or trunk. Comparable to conventional computer-assisted dermoscopy, we used system-integrated overview images of the body and skin areas to make sure that measurements are done in consistent areas. The laser scanning handpiece uses a plastic tip as a distance holder between optical component and skin surface. The distance holder was gently placed onto the skin to avoid pressure- or shear-induced effects on the vessel diameter (28). Terminal hair was carefully trimmed. Scales were not removed. According to the patients' verbal feedback, the OCT scans do not lead to any patient discomfort.

Imaging parameters

Clinical signs such as erythema and skin thickening can result from microvascular changes and epidermal hypertrophy, respectively. Thus, we defined epidermal thickness, vascular density, depth, diameter, and vessel count as imaging parameters for quantification of skin inflammation (**Figure 2**). The calculation of vascular density, depth, and diameter was assisted by the proprietary vessel analysis software (Michelson Diagnostics, Maidstone, Kent, UK). All measures were performed by the same operator.

Epidermal thickness *ET*

We used the integrated on-screen ruler tool to measure the maximum epidermal thickness (*ET*) per image stack, then a mean ET of three image stacks was calculated with standard deviation. ET_L is the epidermal thickness of the target lesion and ET_C of the control at baseline. The same indices were used analogously for the other imaging parameters.

Vascular density ϱ

The vascular density ϱ was calculated at the depth of the superficial plexus. It is the density of the top of the superficial plexus calculated over the depth range, which is the plexus depth ± 60 μm.

Plexus depth θ

The plexus depth θ is the depth of the top of the superficial plexus, where the density reaches 50% of the maximum vessel density.

Vessel diameter δ

The vessel diameter δ is a modal value calculated at the depth of the superficial plexus. It is the diameter of the majority of the vessels.

Vessel count *N*

The vessel count *N* was calculated using ImageJ 1.53k (U.S. National Institutes of Health, Bethesda, MD, USA). We anticipated that the cross sections of the elongated capillaries could be most accurately measured at about 200 μm depth, as the last few *en-face* scans capture undesired projection artifacts from the superficial vessels. The *en-face* images were thresholded and converted into binary images. Adjacent or overlapping vessels were divided by watershed segmentation.

The vessels were counted by automatic particle analyzer using Sobel edge detection.

Response rate

We obtained fit coefficients λ using MATLAB R2021b (The MathWorks, Natick, MA, USA) to fit ET to an exponential equation $ET = A \times \exp(-\lambda \times t) + ET_R$ as a function of time t based on least squares algorithm, where ET_R is the estimated minimum ET during 52 weeks of therapy and A is an adjusting parameter. The number of weeks of therapy t_R required for ET reduction achieving $1.25 \times ET_R$ is then given by $t_R = -\lambda^{-1} \times ln[(k \times ET_R - ET_R)/A]$ for $k = 1.25$. If physiologically achievable, instead of $k \times ET_R$, t_R can also be calculated for $0.5 \times ET_L$ (50% reduction of ET_L from baseline).

Statistical analysis

We used Pearson correlation coefficient r to show the correlation between ET or N and the clinical scores.

Results

Description of patients at baseline

Patient 1 was a 52-year-old male with psoriasis (PASI = 19.5, BSA = 37%) who was treated with ixekizumab. He had no previous systemic therapy.

Patient 2 was a 30-year-old male with psoriasis (PASI = 8.7, BSA = 11%) who received risankizumab. Prior therapies were acitretin, dimethyl fumarate, methotrexate, certolizumab, ustekinumab, and secukinumab.

Patient 3 was a 45-year-old male with psoriasis (PASI = 10.8, BSA = 10%) who underwent therapy with certolizumab. He was previously treated with methotrexate.

Patient 4 was a 50-year-old female with atopic dermatitis (EASI = 17, BSA = 25%) who was treated with dupilumab. She had no previous systemic therapy.

In patient 1 and 2, the target lesions were located on their right arms. In patient 3 and 4, the target lesions were located on their trunk. The control area was their perilesional skin.

Structural imaging parameters

Epidermal thickness

In line with clinical and histopathological findings, at baseline we measured a thicker ET_L in psoriasis due to hyperkeratosis (Figure 3, top). A similar observation was made in atopic dermatitis where the increased ET_L was due to spongiosis and/or lichenification (Figure 3, bottom). At baseline, the mean ET_L was 405.8 μm (±20.8 μm) in psoriatic skin and 270 μm (±25.5 μm) in atopic dermatitis. ET_C ranged from 90 to 110 μm and was similar in uninvolved skin of patients with psoriasis and atopic dermatitis. The thickened ET_L decreased during the observation period under therapy (Figure 4, row 1). According to t_R, $0.5 \times ET_L$ was achieved as follows: ixekizumab (after 3.95 weeks), certolizumab (after 4.23 weeks), risankizumab (after 6.08 weeks), and dupilumab (after 22.13 weeks). $1.25 \times ET_R$ was achieved as follows: ixekizumab (after 4.31 weeks), certolizumab (after 6.52 weeks), risankizumab (after 11.23 weeks), and dupilumab (after 33.89 weeks).

In good agreement with the OCT measurements, the clinical severity was reduced in the target lesion (TSS) and in the global assessment (PASI or EASI) (Supplementary Figure 1). A positive correlation was observed between ET_L and clinical scores as follows: ixekizumab ($r_{TSS} = 0.83$, $p = 0.0208$; $r_{PASI} = 0.9564$, $p = 0.0007$), certolizumab ($r_{TSS} = 0.8857$, $p = 0.008$; $r_{PASI} = 0.9265$, $p = 0.0027$), risankizumab ($r_{TSS} = 0.8968$, $p = 0.0062$; $r_{PASI} = 0.8017$, $p = 0.0301$), and dupilumab ($r_{TSS} = 0.9778$, $p = 0.0007$; $r_{EASI} = 0.9184$, $p = 0.0097$).

Decay rate

The decrease of ET_L under therapy yielded the following decay rates: ixekizumab ($\lambda = 0.4418$, $R^2 = 0.96$), certolizumab ($\lambda = 0.3224$, $R^2 = 0.95$), risankizumab ($\lambda = 0.2117$, $R^2 = 0.96$), and dupilumab ($\lambda = 0.05817$, $R^2 = 0.93$). In this comparison, the highest rate was observed for ixekizumab followed by certolizumab and risankizumab. The decay rate under dupilumab was a factor of 3.6–7.6 slower than the biologic therapies of psoriasis.

Vascular imaging parameters

Vascular patterns and shapes

We used the terminology as proposed by Ulrich et al. (15). Characteristic vascular patterns and shapes were visible in the *en-face* mode at about 200 μm depth (Supplementary Figure 2). Psoriatic skin exhibited "dotted" or "pinpoint-like" vessels resulting from vessel elongation within extended dermal papillae. Lichenification is often observed in chronic eczema. Coarsening and wrinkling of the lichenified skin may change the direction of the capillary loops causing a striped pattern. Thus, "comma-like" vessels were observed in atopic dermatitis. Uninvolved skin typically has "linear" vessels generating a reticular pattern.

Vascular density, plexus depth, and vessel diameter

Vascular parameters decreased or normalized during therapy course (Figure 4, rows 2–4). Before treatment the mean

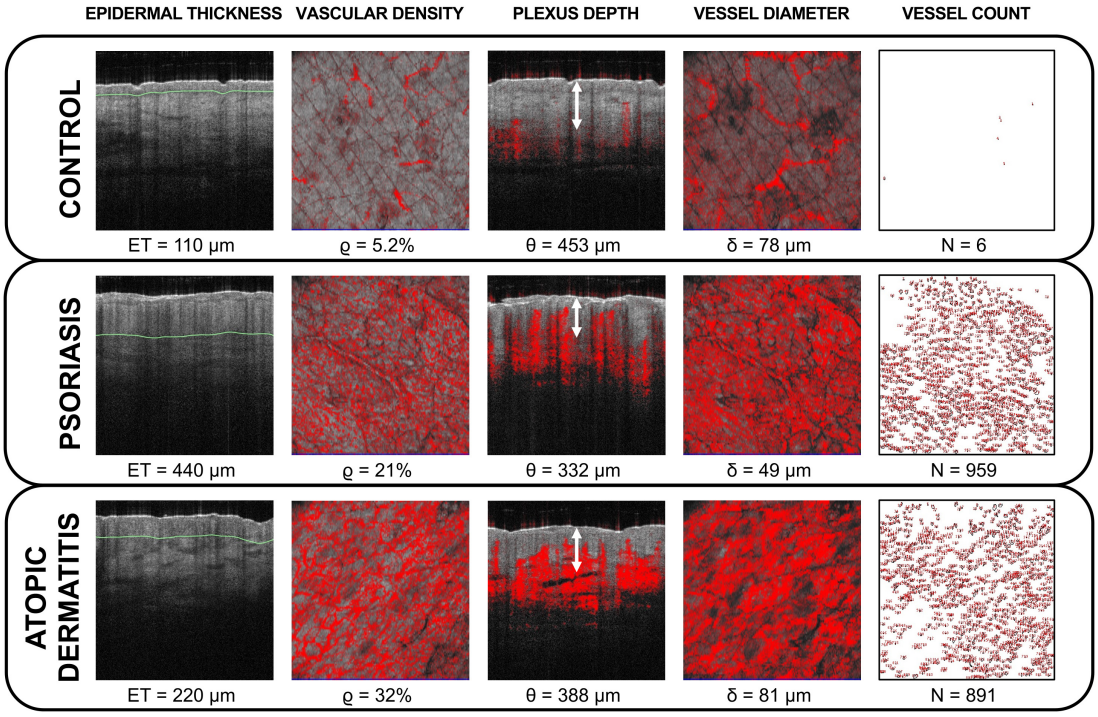

FIGURE 2
Optical coherence tomography (OCT) imaging parameters for objective quantification of skin inflammation. Epidermal thickness (*ET*), vascular density ϱ, plexus depth θ, vessel diameter δ, and vessel count *N* were calculated in unaffected skin (control) and in target lesions (psoriasis and atopic dermatitis) at baseline. Lesional inflammatory skin exhibited increased epidermal thickness denoted by green lines and alterations in vasculature in comparison to control sites. The vascular density is exemplarily shown at 400 µm depth and the vessel diameter is shown at 600 µm depth. The plexus depth is indicated by white arrows. The vessel count was performed at 200 µm depth.

ϱ_L in psoriatic skin was 4.6% (±1.9%), which was higher than ϱ_C with 2.1% (±1.23%). ϱ_L in atopic dermatitis was 24.5% (±8.4%), while ϱ_C was 6.3% (±1.24%). The higher ϱ_L from baseline decreased after therapy start as a result of reduction in vessel diameter and/or vessel count (**Supplementary Figure 3**).

We defined the location of the origin (0,0) in the upper left of the image according to the general convention in image processing. This means that plexus depth and optical axis *z* have the same direction. For plots, the origin is located in the lower left. We observed an upward shift of the plexus $\Delta\theta = \theta_L$-θ_C by −83.4 µm (± 42.3 µm) in psoriatic skin θ_L when compared to θ_C. At baseline, the mean δ_L in psoriatic skin was 35.2 µm (± 6.9 µm), which was smaller than δ_C with 58.6 µm (±26.8 µm). We did not observe an upward shift in the patient with atopic dermatitis. In contrast to the psoriatic lesions, in atopic dermatitis δ_L was 81 µm (±3.1 µm), which was larger than δ_C with 57.7 µm (±6.9 µ m).

Vessel count

The mean N_L in psoriasis and atopic dermatitis was 531.4 (±285.9) and 987 (±37.5), respectively. The mean N_C was 35.08 (±14.27). After 52 weeks, we observed a full normalization of the vessel count (**Figure 4**, row 5).

Also, a positive correlation was observed between *N* and clinical scores as follows: ixekizumab (r_{TSS} = 0.85, p = 0.0154; r_{PASI} = 0.9589, p = 0.0006), certolizumab (r_{TSS} = 0.8978, p = 0.0061; r_{PASI} = 0.9327, p = 0.0022), risankizumab (r_{TSS} = 0.6055, p = 0.1497; r_{PASI} = 0.6792, p = 0.0933), and dupilumab (r_{TSS} = 0.9378, p = 0.0057; r_{EASI} = 0.9272, p = 0.0078).

Clinical response

The results of this case series indicated a good correlation with the clinical scores. A 75% reduction from baseline in the TSS (TSS-75) was achieved under ixekizumab after 3 weeks and under certolizumab after 3.5 weeks. In this observation period, TSS-75 under risankizumab was not achieved. After 3 weeks, TSS-75 was achieved under dupilumab.

Discussion

Optical coherence tomography is a suitable imaging tool for the investigation and monitoring of inflammatory skin diseases. The VivoSight OCT offers user-friendly handling and fast scanning, which is important for its application as

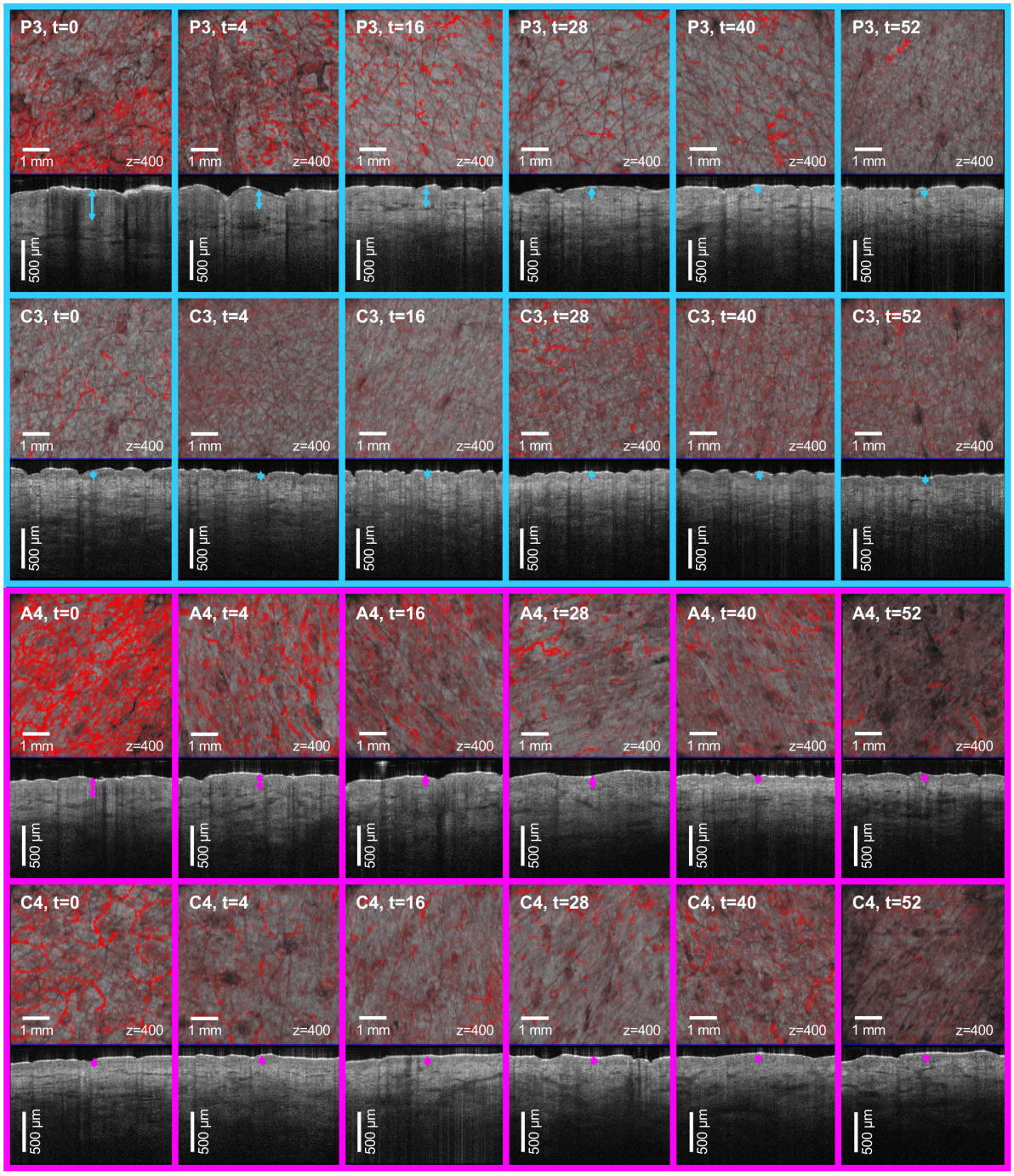

FIGURE 3
Optical coherence tomography (OCT) guided monitoring of biologic therapy in psoriasis and atopic dermatitis. Patient 3 with psoriasis (P3) was treated with certolizumab (top) and patient 4 with atopic dermatitis (A4) was treated with dupilumab (bottom) for *t* = 52 weeks. The vertical B-scans and the corresponding *en-face* scans at 400 µm depth were collected in the course of therapy. Hyperkeratotic psoriatic plaques led to a signal reduction at baseline. Under therapy a decrease of the epidermal thickening (arrows) and a normalization of the vascularization (red signal) were observed in psoriasis and atopic dermatitis. No significant changes were detected in the control sites (C3 and C4).

a bedside monitoring device. But the system applied in this study has a limited resolution capacity that does not allow the detection of single cells. In comparison, the investigational line-field confocal OCT provides superior axial resolution of 1.1 µm and lateral resolution of 1.3 µm (29). This would allow a characterization of individual cells and microstructures

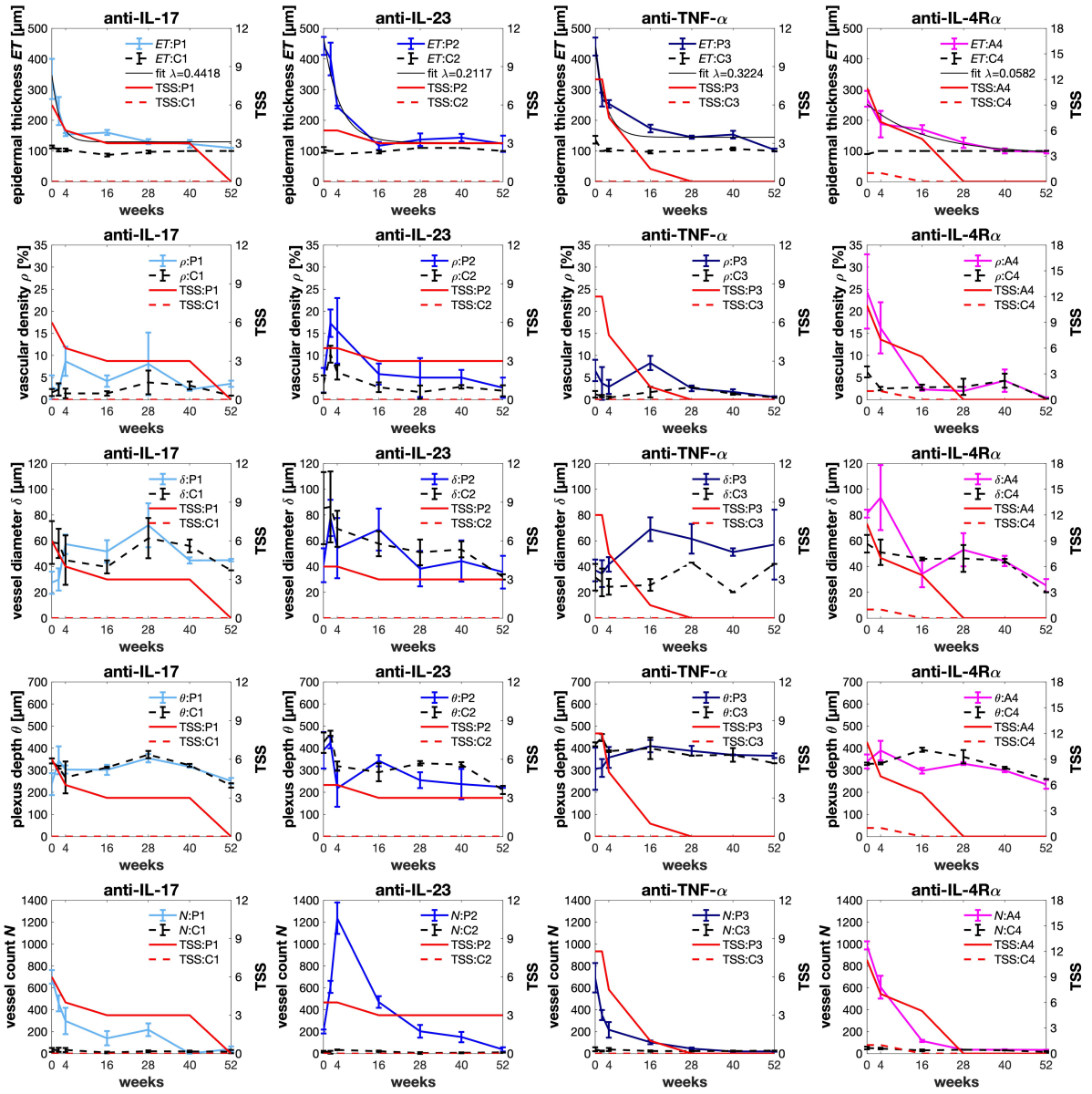

FIGURE 4
Monitoring therapy response using optical coherence tomography (OCT). In psoriasis (P1–P3) and atopic dermatitis (A4), the epidermal thickness (*ET*) was fitted to calculate the exponential decay rate or response rate λ. The vessel count *N* was calculated using ImageJ (U.S. National Institutes of Health, Bethesda, MD, USA). After 52 weeks of treatment, we observed a full normalization of the increased epidermal thickness and the vessel count. The vascular parameters such as vascular density ϱ, vessel diameter δ, and plexus depth θ were calculated by using the proprietary VivoSight vessel analysis software (Michelson Diagnostics, Maidstone, Kent, UK). Prior to treatment, the vascular density in inflamed skin was higher than in the control areas. Interestingly, we observed an upward shift of the plexus depth and smaller vessel diameters in psoriatic skin in comparison to the control at baseline. Eczematous skin showed larger vessel diameters. As a potential sign of therapy response, the vascular parameters normalized during therapy course. For correlation, the total sign score (TSS) was used to clinically assess the target lesions and their control sites. For psoriasis, erythema *E*, induration *I*, and desquamation *D* were assessed using a 5-point scale (0–12). For atopic dermatitis, six clinical signs including erythema *E*, papulation *I*, excoriation *Ex*, lichenification *Li*, crusting *C*, and dryness *Dr* were graded using a 4-point scale (0–18).

in inflammatory skin diseases (30). Furthermore, OCT with dynamic contrast allows color-coding of different epithelial cell layers based on micromotions of cellular structures (31, 32). So far, these technical upgrades have not yet been incorporated into a clinically approved OCT system for dermatological applications. The future goal is to obtain contactless, whole body scans *via* rapid scanning of large body sites as commercial OCT systems only provide small fields of view (33, 34). To date, we

are dependent on the selection of target lesions for imaging. While psoriatic lesions tend to recur at the same skin sites that were affected previously, in atopic dermatitis the eczema lesions tend to shift location. Under this aspect, monitoring of target lesions could potentially miss an eczema flare or even psoriasis that exacerbates on a different body part.

Psoriasis and atopic dermatitis are associated with lower skin hydration (35, 36). Consequently, effects of laser-tissue interactions such as scattering (e.g., scaling, hyperkeratosis, and lichenification) and shielding (e.g., shadow artifacts caused by hair or crusts) could lower optical penetration and might masquerade as a loss of perfusion.

In an attempt to define imaging biomarkers for inflammatory skin diseases, we demonstrated the application of OCT for monitoring biologic therapy in psoriasis and atopic dermatitis based on four case studies. Biomarkers are objective, quantifiable, and reproducible (37). We should differentiate between robust and weak imaging biomarkers. Robust biomarkers might be *ET* and *N*, as these parameters are less influenced by internal and external factors. In this study, manual measurements of the maximum *ET* still remain vulnerable to intraobserver variability, which was minimized by repeated measurements. Hence, further studies should incorporate computer-assisted analysis of the *ET*. Weaker biomarkers such as ϱ and δ might be highly influenced by internal stress factors of the subject (comparable to the "white coat effect") and outdoor temperatures (hot temperatures lead to vasodilation and cold temperatures lead to vasoconstriction) as we observed intraindividual variations in control sites.

In this work, we provided a detailed description on vascular alterations in psoriasis and atopic dermatitis compared to non-lesional skin. Our findings were consistent with previous observations reported on higher vascularization and characteristic vascular pattern in psoriasis (16–18). While "dotted" vessels were previously described in psoriasis (38), we firstly described the appearance of "comma-like" vessels in atopic dermatitis with lichenification. We detected an upward shift of the plexus in psoriasis. We anticipated that a plexus shift results from an elongation of the capillary loops, which is more distinctive in severe psoriasis. At baseline, no shift of the plexus depth was observed in our patient with atopic dermatitis. Byers et al. (22) described deeper vascular layers in atopic dermatitis so that we need to make further investigations before coming to a conclusion. We observed large vessels and high vascular densities in atopic dermatitis that were consistent with former studies (38, 39). Manfredini et al. (23) reported on a reduction of dermal edema and vascularization under dupilumab. In our analysis, we also observed a normalization of the vasculature under therapy. Further, we observed that vessel elongation in psoriasis appeared with smaller capillary loop diameters. Evidently, a larger case number is required to confirm our preliminary observations.

The aim of biologic treatment especially in atopic dermatitis is to improve the skin barrier. We observed a good correlation between *ET* and TSS. Our results on the decrease of *ET* under therapy were in good agreement with previous studies using topical (25, 40) and non-biologic systemic therapies (19). In contrast to conventional therapies of psoriasis, we observed an accelerated decrease of *ET*. Similar results on *ET* in atopic dermatitis were reported under dupilumab (23). We also anticipated that *ET* may be a robust imaging biomarker as already stated by Byers et al. (22). The rapid decrease in *ET* can be regarded as an exponential decay. We interpreted the decay rate λ as a response rate. In theory, $\lambda = 0$ means steady state. Values of $\lambda > 0$ implicate therapy response meaning the larger λ the higher the response. $\lambda < 0$ refers to therapy failure.

Patient 2 was bio-experienced with a long record of pretreatments, therefore, a slower therapy response in TSS was seen under risankizumab. Interestingly, in patient 4 with atopic dermatitis higher vessel density and diameter were observed in the control area at baseline indicating subclinical inflammation in clinically healthy-appearing skin. In addition, although a rapid improvement of patient 4 was clinically observed shown as TSS-75 after 3 weeks, using OCT we were able to detect a prolonged epidermal thickening for $t_R(1.25 \times \mathrm{ET}_R) = 33.89$ weeks as a sign of persistent disease activity. Comparable observations were reported by Byers et al. (22). The understanding of subclinical inflammation highlights the importance of therapy continuation to avoid the risk of relapse (41).

Conclusion

Preliminary observations of this work showed that OCT may be suitable for objective quantification of structural (epidermal thickness) and vascular parameters (vascular density, depth, diameter, and count). These parameters may serve as objective imaging biomarkers for monitoring therapeutic effects in psoriasis and atopic dermatitis. The relatively short acquisition time of OCT is an important demand for medical imaging to minimize time burden for patients.

Therapy response may be characterized by reduction of epidermal thickness and normalization of vascular network. Potential imaging biomarkers such as epidermal thickness and vessel count exhibited rapid changes. The calculated response rate λ may serve as a useful parameter in the assessment of therapeutic effects. Additional diagnostic value of OCT angiography could be seen in the detection of subclinical inflammation that implicates the need for therapy continuation beyond clinical remission.

In this preliminary evaluation, all patients have responded well to their systemic treatment. In the next step, we will also evaluate insufficient therapy responses or therapy failures in a large prospective, long-term, observational study. Additional imaging biomarkers revealing desquamation, excoriation, and lichenification should be considered in

upcoming studies. The vision of the future is to provide "OCT-guided therapy" enhancing the current dermatological assessment and contributing to personalized medicine.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Lübeck, Germany. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LH-W and HY contributed to data acquisition. LH-W performed the data analysis and wrote the main manuscript text. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This project was supported by the Clinician-Scientist-Program (LH-W) and by structured funding of the Cluster of Excellence EXC2167 "Precision Medicine in Chronic Inflammation." We acknowledge financial support by Land Schleswig-Holstein within the funding program "Open Access Publikationsfonds."

Conflict of interest

Author DT declares being a consultant, investigator, speaker, and participating in scientific advisory boards for AbbVie, Almirall, Amgen, Biogen Idec, Eli Lilly, Galapagos, Janssen-Cilag, LEO Pharma, MSD, Novartis, Pfizer, Regeneron, Samsung, Sanofi, and UCB; and research/educational grants from AbbVie, LEO Pharma, and Novartis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.995883/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 20 October 2022
DOI 10.3389/fmed.2022.1001120

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 22 July 2022
ACCEPTED 12 September 2022
PUBLISHED 20 October 2022

CITATION
Didona D, Sequeira Santos AM, Cunha T, Hinterseher J, Kussini J and Hertl M (2022) Case report: Detection of anti-bullous pemphigoid antigen 180 antibodies in a patient with Behçet's disease.
Front. Med. 9:1001120.
doi: 10.3389/fmed.2022.1001120

Case report: Detection of anti-bullous pemphigoid antigen 180 antibodies in a patient with Behçet's disease

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Behçet's disease (BD) is a systemic inflammatory disease of unknown etiology. BD is characterized by relapsing oral and genital ulcers, several different cutaneous features, relapsing bilateral uveitis, and involvement of internal organs, showing vascular, gastrointestinal, and neurological manifestations. Serologically, BD is not characterized by disease-specific autoantibodies. In fact, only laboratory markers of inflammation, such as C-reactive protein, may be increased in association with increased disease activity. Bullous pemphigoid (BP) is an autoimmune disease characterized mainly by tense blisters and urticaria-like plaques on the skin. In addition, BP can involve oral mucosa in up to 20% of patients. Patients with BP show serum IgG autoantibodies against BP antigen 180 (BP180) and/or BP antigen 230 (BP230). Tissue-bound autoantibodies can be visualized as linear IgG staining along the basement membrane by direct immunofluorescence microscopy. In this report, we first described a young patient with BD who showed IgG autoantibodies against BP180 without developing blisters or urticaria-like plaques.

KEYWORDS

Behçet's disease, bullous pemphigoid, diagnosis, epitope spreading, autoantibodies

Introduction

Behçet's disease (BD) is characterized mainly by recurrent oral aphthae and relapsing genital ulcerations (1). Furthermore, several other manifestations, such as relapsing bilateral uveitis, different skin lesions, arthritis, and involvement of internal organs are described in patients with BD (1). BD is more common along the ancient silk road, which extends from eastern Asia to the Mediterranean, and it is more frequent in Turkey,

showing an prevalence of between 80 and 420 cases per 100,000 inhabitants, while the prevalence ranges from 1 per 15,000 to 1 per 500,000 inhabitants in the United States (2). The onset of BD typically occurs in the third or fourth decade of life, and it is rarely diagnosed in patients over the age of 50 years (2). An association between BD and human leukocyte antigen (HLA-B51) has been widely described (2). Recurrent oral and genital ulcerations represent the clinical hallmark of BD (1). Cutaneous lesions occur in more than 70% of patients with BD and include acneiform lesions, papulopustular eruptions, pseudofolliculitis, nodules, septal panniculitis, pyoderma gangrenosum-like lesions, and palpable purpura (1). The diagnosis of BD can be made only on the basis of the clinical findings (**Table 1**) (3). Indeed, laboratory tests are not pathognomonic for BD (2). According to the International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD), patients with a score of <3 are not affected by BD, patients with a score of 3 are considered probably affected by BD, and patients with a score of ≥ 4 have a definitive diagnosis of BD (**Table 1**) (3).

Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease in adult patients (4). It usually affects elderly patients between 60 and 80 years old (4). It is estimated that up to 13 new cases per 1000,000 inhabitants are diagnosed every year (4). The main clinical features of BP are severe pruritus and tense blisters on erythematous skin (5). Pruritus may be an important clinical indicator of a pre-clinical stage of BP (4). Indeed, a subset of elderly patients with pruritus may show serum IgG autoantibodies against BP antigen 180 (BP180) and/or BP antigen 230 (BP230), while chronic pruritus is increased in the elderly population (6). The serological hallmark of BP is represented by IgG autoantibodies against hemidesmosomal proteins of the skin and mucous membranes, namely BP180 and BP230 (7). Furthermore, patients with BP patients show linear IgG and/or C3 staining along the basement membrane by direct immunofluorescence (DIF) on perilesional skin (7). The exact process that leads to the loss of self-tolerance and the production of autoantibodies is still unknown, but several factors, such as environmental factors, drug intake, radiation therapy, and trauma, may have a role in the pathogenesis of BP (5).

TABLE 1 Diagnostic criteria for Behçet's disease (BD) according to the International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) (3).

Sign/Symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test*	1

*Pathergy test is optional.

Case description

A 36-year-old Caucasian male was admitted to our department because of recurrent oral and genital ulcerations (**Figures 1A,B**). Furthermore, he showed an acneiform eruption on his back that was recalcitrant to topical and systemic therapy with erythromycin (**Figure 1C**). Routine laboratory parameters did not show any alterations, and the serological test for hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and syphilis were negative. A microbial analysis of swabs from lesions on the back did not detect any microbial infections. Furthermore, swabs from oral ulcerations did not detect herpes simplex virus (HSV)-1, HSV-2, cytomegalovirus, coxsackievirus, or oral candidiasis. A punch biopsy from oral ulceration showed a massive infiltration of neutrophils, lymphocytes, and plasma cells (**Figure 1D**). DIF on perilesional oral mucosa did not show any deposition of IgG or C3 (**Figure 1E**). Furthermore, indirect IF (IIF) on the monkey esophagus did not show IgG deposition (**Figure 1F**). However, repeated ELISA analysis (Euroimmun, Lübeck, Germany) on serum detected IgG autoantibodies against BP180 at every follow-up visit (for a total of eight times) ranged between 37 and 48 RU/ml. Noteworthy, previous ELISAs performed in other clinics did not detect any autoantibodies against BP180. To confirm our serological findings, we performed Western blotting that detected a reactivity against both intracellular and extracellular BP180 subdomains (**Supplementary Figure 1**). Therefore, according to the clinical and histological features, a diagnosis of BD was made (ITR-ICBD-Score: 5). The patient was in follow-up for 18 months and he did not develop any blisters on the skin. Furthermore, we performed DIF two times, which were both negative. In addition, IIF was repeated at every follow-up visit (for a total of eight times), showing always negative results.

Discussion

BD is an inflammatory disease characterized by polymorphous clinical features. BD is also known as a "silk route disease" because its incidence is higher in regions along this ancient commercial route (2). Indeed, the incidence of BD varies according to the geographical area (2). The highest prevalence has been reported in Turkey (up to 420 cases per 100,000 inhabitants per year), while a lower prevalence has been reported in the United Kingdom, Spain, Sweden, Portugal, and the United States, ranging from 0.3 to 6.4 cases per 100,000 inhabitants (2). A strong association between BD and HLA-B51

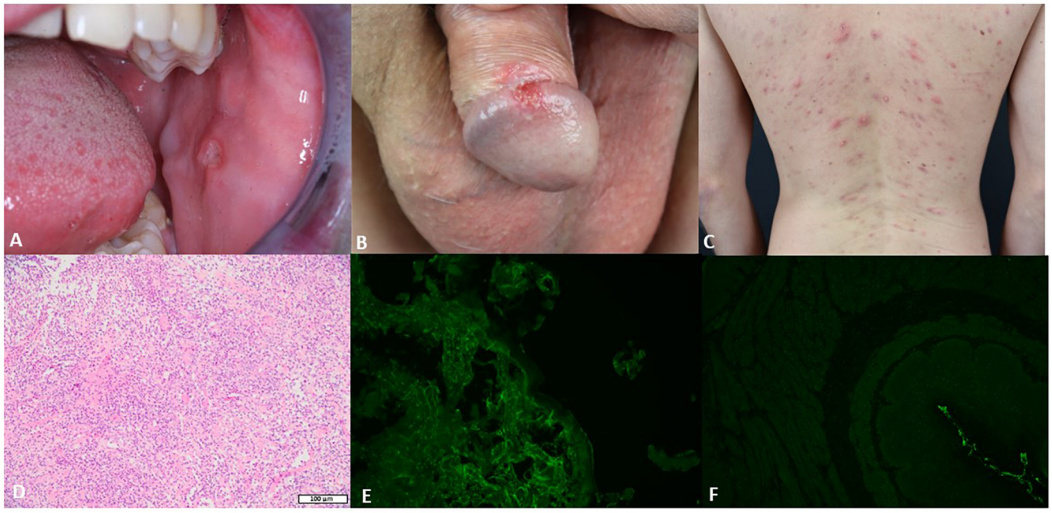

FIGURE 1
The clinical, histological, and serological features of the patient. **(A)** Single buccal erosion with a sharp border. **(B)** Erosion on the penis with a sharp border. **(C)** Acneiform eruption with sterile pustules. **(D)** Biopsy from the oral ulceration with a massive infiltration of neutrophils, lymphocytes, and plasma cells (H&E 10×). **(E)** Negative direct immunofluorescence (DIF) on a biopsy from the oral mucosa. **(F)** Negative indirect immunofluorescence (IIF) on monkey esophagus.

has been observed (2). BD etiology is unknown, but the strong association with HLA-B51 suggests that genetic background plays a pivotal role in its pathogenesis (8). Furthermore, the environment and several microorganisms, such as HSV-1 and *Streptococcus sanguis,* maybe involved in the pathogenesis of BD (8). In addition, γδT cells, cytotoxic T cells, Th1 cells, regulatory T cells, and more recently Th17 cells have been shown to be involved in the pathogenesis of BD (8). Since there are no pathognomonic laboratory tests to diagnose BD, the diagnosis is based on clinical criteria (**Table 1**) (3). Clinically, BD has a relapsing-remitting course, and its hallmarks are represented by recurrent oral and genital ulcerations (1). Furthermore, ocular, cardiovascular, articular, neurological, and gastrointestinal manifestations are commonly reported and they can occur simultaneously or not (1). Therefore, the diagnosis of BD is tricky. Several differential diagnoses should be considered, such as inflammatory bowel diseases, systemic lupus erythematosus, recurrent aphthous stomatitis, pemphigus vulgaris, mucous membrane pemphigoid (MMP), and BP. BP is serologically characterized by IgG antibodies directed against hemidesmosomes, namely BP180 and BP230 (7). Furthermore, a correlation between antibodies against BP180 and clinical activity has been reported (9). The diagnosis of BP relies on clinical features, histological findings, and the detection of autoantibodies against BP180 and/or BP230 by ELISA, DIF, and/or IIF (7). MMP belongs to pemphigoid diseases and its mean age of onset is in the seventh decade of life (4). MMP is characterized mainly by oral erosions (85% of cases) and the involvement of the conjunctiva (up to 65% of cases) (5). In patients with MMP, IgG antibodies against BP180 and BP230 are mostly detected by ELISA (4, 5). In contrast to BP, MMP shows reactivity against the C-terminal epitopes of BP180 rather than the BP180 NC16A domain (4). In our case, the patient showed IgG autoantibodies against BP180 by ELISA, without the detection of IgG by IIF or DIF. Furthermore, the clinical and histological features were not representative of BP. In addition, our patient was 36 years old at the time of the diagnosis, while BP and MMP usually affect elderly people. Epitope spreading (ES) is the diversification of B- and/or T-cell responses from an initial dominant epitope to a secondary epitope over time (10). The intramolecular ES is described as the diversification of immune response in the same autoantigen, whereas the intermolecular ES involves different antigens of a single complex or that colocalize in the same anatomical site (10). In our case, the patient has developed anti-BP180 IgG autoantibodies over 2 years without showing any clinical or histopathological findings for BP. Indeed, it has been widely described that chronic inflammation, as in recurrent ulcerations, can lead to ES (10). Intramolecular and intermolecular ES have been widely reported in patients with autoimmune blistering diseases (10–12). Furthermore, in a previous research, we detected Th17 cell responses against BP180 in some elderly patients with pruritus, showing that chronic inflammation and inducing the production of pro-inflammatory cytokines and proteolytic enzymes can lead to the production of IgG serum autoantibodies against BP180 through unmasking epitopes on hemidesmosome (6). To the best of our knowledge, this is the first account of the detection of anti-BP180 IgG antibodies in a patient with BD.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

DD and TC: concept and writing. JH and JK: pictures. MH: editing. All authors contributed to the article and approved the submitted version.

Funding

This article was supported by grants from FOR 2497 Pegasus to MH.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1001120/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Western blotting showing reactivity against extracellular and intracellular subdomains of BP180.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 24 October 2022
DOI 10.3389/fmed.2022.975754

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 22 June 2022
ACCEPTED 10 October 2022
PUBLISHED 24 October 2022

CITATION
Lin W-C, Hsieh T-S and Chu C-Y (2022) Case report: Development of vanishing bile duct syndrome in Stevens-Johnson syndrome complicated by hemophagocytic lymphohistiocytosis.
Front. Med. 9:975754.
doi: 10.3389/fmed.2022.975754

Case report: Development of vanishing bile duct syndrome in Stevens-Johnson syndrome complicated by hemophagocytic lymphohistiocytosis

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Background: Vanishing bile duct syndrome is a rare drug-induced disease characterized by cholestasis and ensuing ductopenia. Dermatological manifestations of drug hypersensitivity such as Stevens-Johnson syndrome and toxic epidermal necrolysis may also present in such cases. Hemophagocytic lymphohistiocytosis is a hyperimmune response caused by unchecked stimulation of macrophages, natural killer cells, and cytotoxic T lymphocytes.

Case presentation: We report a severe case who presented with concurrent Stevens-Johnson syndrome and vanishing bile duct syndrome complicated by hemophagocytic lymphohistiocytosis after the ingestion of non-steroidal anti-inflammatory drugs. Despite the fact that improvements in vanishing bile duct syndrome can be assumed when combining the clinical lab data clues, as well as repeated liver biopsies showing recovering ductopenia, the patient developed hypovolemic shock combined with septic shock episodes and died on day 236.

Conclusion: To our knowledge, this is the fifteenth report of vanishing bile duct syndrome associated with Stevens-Johnson disease or toxic epidermal necrolysis. Mortality rate remains high without treatment guidelines established due to the rarity and heterogenicity of the population. Further studies are needed to identify possible risk factors, prognostic indicators, and the standard of care for vanishing bile duct syndrome associated with Stevens-Johnson disease or toxic epidermal necrolysis.

KEYWORDS

allergy, non-steroidal anti-inflammatory drugs, drug-induced liver injury, vanishing bile duct syndrome, Stevens-Johnson syndrome, hemophagocytic lymphohistiocytosis

Introduction

Vanishing bile duct syndrome (VBDS) is an uncommon but serious consequence of drug-induced liver injury. It presents clinically as chronic cholestasis and histologically as ductopenia (>50% disappearance of the bile duct in identified portal tracts) (1). Stevens–Johnson syndrome (SJS) is a rare and severe dermatological condition attributed

primarily to a T cell-mediated hypersensitivity reaction mostly induced by drugs (2). Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder that may cause multi-organ failure resulting from uncontrolled activation of macrophages, natural killer (NK) cells, and cytotoxic T lymphocytes (3).

We report a rare and difficult case of a 42-year-old male who presented with concurrent SJS and VBDS complicated by HLH.

Case description

A 42-year-old male with a reported history of resolved hepatitis C was admitted to hospital due to fever and sore throat for 9 days, combined with a generalized rash over the entire body for 5 days.

The patient had not taken new medications in the recent 2 months until 8 days prior to this admission, when the patient visited a local clinic for flu-like symptoms of fever, sore throat, and general malaise combined with muscle weakness and was prescribed non-steroidal anti-inflammatory drugs (NSAIDs)—mefenamic acid and diclofenac—for 3 days with acetaminophen and famotidine. However, the fever persisted despite the treatment, with subsequent development of itchy erythematous macules and papules spreading from the face and trunk to the extremities 5 days prior to this admission. Associated symptoms of ophthalmalgia, conjunctival injection, and lip swelling were also noted. After revisiting the local clinic and obtaining an additional prescription for ibuprofen, he visited the emergency department of another hospital 4 days prior to this admission, where numerous confluent erythematous to purpuric macules and patches on the face, trunk, and extremities, with variously sized erosions arising from the erythematous base were seen. The diagnosis of SJS was thus confirmed. The patient was then transferred to our hospital for further treatment.

On admission to our hospital, the patient was clear and oriented, with stable vital signs. Physical examinations showed that generalized confluent erythematous to purpuric macules and patches were distributed on the face, trunk, and limbs, with some flat erythematous spots present on the distal extremities. A sum of erythema of 35% total body surface area (TBSA) with blistering of 8% TBSA was calculated after the RegiSCAR review. Mucosal involvement with the presence of conjunctival and oral ulcers were also noted (Figure 1). Viral panel, mycoplasma pneumoniae infection and autoimmune survey yielded negative results (Supplementary Tables S1, S2).The skin lesions gradually improved to brownish and scaly characteristics, with near resolution noted at around day 14 under treatment with systemic corticosteroids (intravenous methylprednisolone), equivalent to 1.2–2.6 mg/kg of prednisone per day, combined with topical antibiotic ointments. Further laboratory examination revealed progressively elevating liver function enzymes and jaundice on day 6 of hospitalization (AST/ALT: 581/1488 U/L; ALP/GGT: 667/1990 U/L; T-Bil/D-Bil: 19.81/15.35 mg/dl) (Figure 2). Elevated IgG, C3, and C4 levels were also noted, without evidence of viral hepatitis. A liver biopsy was thus performed on day 6, and showed cholestatic hepatitis with marked perivenular cholestasis, ballooning of hepatocytes, and Councilman bodies with microgranulomas. Aggregation of histiocytes, neutrophils, and eosinophils were seen in the hepatic lobules. In a total of 10 portal tracts, only three bile ducts survived, which showed degeneration and cell senescence changes (i.e., increased nuclear to cytoplasm ratio, uneven nuclear spacing, drop-out, and syncytia formation; Figures 3A,B). VBDS was thus diagnosed. Due to progression of cholestasis and hepatitis on day 12 (AST/ALT: 973/2455 U/L; ALP/GGT: 815/3165 U/L; T-Bil/D-Bil: 34.91/22.81 mg/dl), systemic corticosteroids were up-titrated to the equivalent of 2.6 mg/kg of prednisone per day, with the capsule form of mycophenolate mofetil initiated at 250 mg twice a day and later up-titrated to 750 mg twice a day. Evaluation for possible liver transplantation was arranged after discussion with the patient and family.

The patient completed pre-transplantation evaluation uneventfully. A significant decrease in liver enzymes and bilirubin levels was observed on day 28 (AST/ALT: 184/647 U/L; GGT: 1,131 U/L; T-Bil/D-Bil: 25.58/15.18 mg/dl). The patient showed resolution of SJS with scars remaining on his extremities and denied discomfort. However, the patient showed a gradual decrease in the hemoglobin level to 8.7 g/dl on day 34, with subsequent discovery of cytomegalovirus (CMV) infection *via* colonoscopy biopsy and blood tests (a CMV viral load of 1,040,000 cp/ml was detected on day 42). Ganciclovir was thus initiated for treatment. Due to the presence of nucleated red blood cells in peripheral blood and the pathological finding of sinus histiocytosis with hemophagocytosis in specimens of the small intestine, a bone marrow study was conducted on day 58.

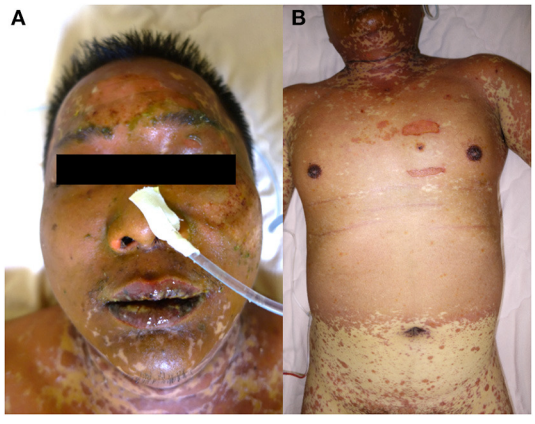

FIGURE 1
Skin manifestations of a 42-year-old male. **(A)** Diffused erosions covered by crusts on the lips. **(B)** The erythematous vesiculobullous rash had spread to the entire body, along with epidermal detachment.

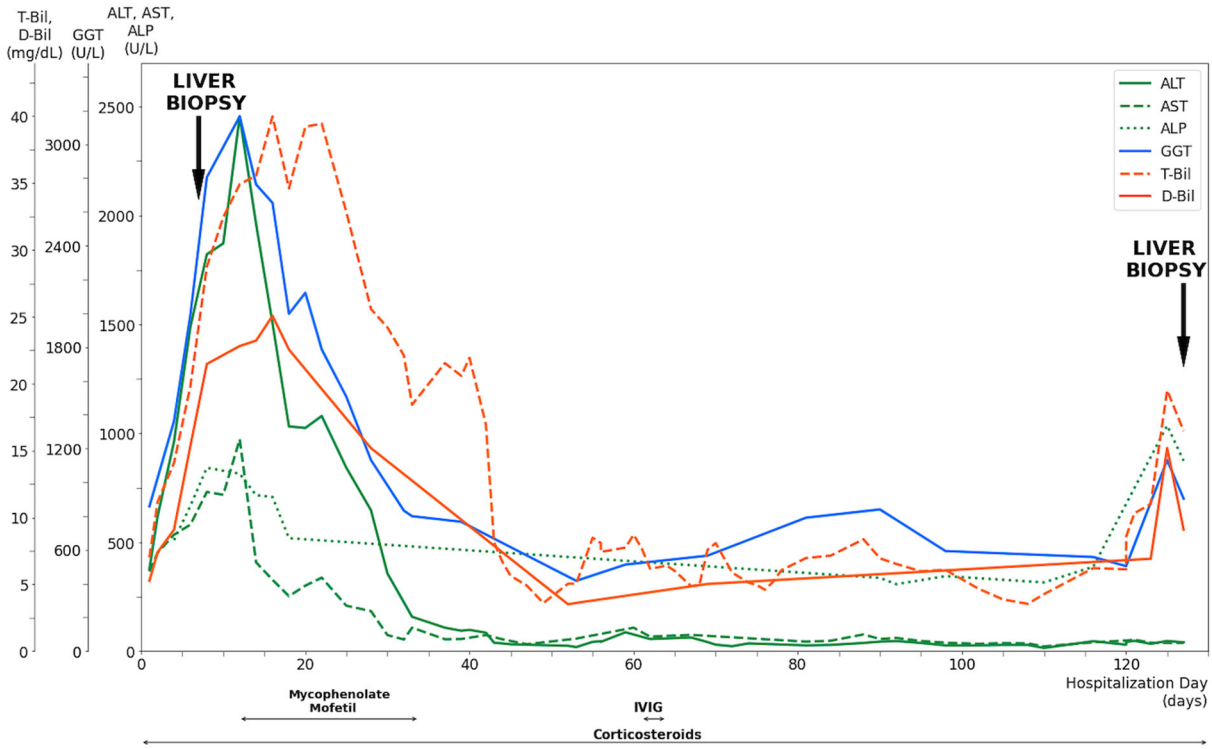

FIGURE 2
Evolution of serum liver tests and medications of a 42-year-old male after exposure to NSAIDs. Corticosteroids were given since the diagnosis of Stevens-Johnson Syndrome with titration according to the clinical presentation. The progressive elevation of liver enzymes and jaundice had led to a liver biopsy performed on day 6, along with the confirmed diagnosis of vanishing bile duct syndrome. Mycophenolate mofetil was prescribed after the diagnosis while the patient prepared for liver transplantation, which was not performed due to deterioration of clinical conditions. Intravenous immunoglobulin was administered for 3 days after the bone marrow biopsy revealed hemophagocytic lymphohistiocytosis. The liver enzymes and bilirubin levels remained relatively stable until day 125, when significant elevation was observed. Repeated liver biopsy was performed on day 127, which showed vanishing bile duct syndrome in resolution. T-Bil, total bilirubin level; D-Bil, direct bilirubin level; GGT, gamma glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; IVIG, intravenous immunoglobulin.

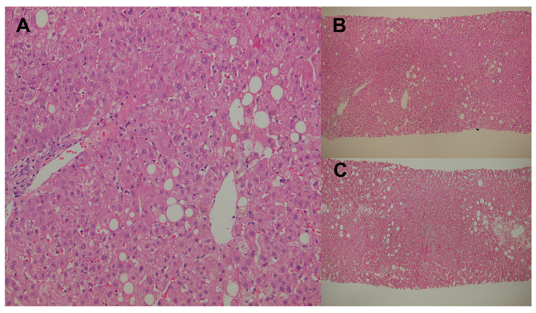

FIGURE 3
Percutaneous liver biopsies. **(A)** Cholestatic hepatitis with marked perivenular cholestasis and ballooning of hepatocytes seen under high-power field hematoxylin and eosin (H&E) staining. **(B)** Initial liver biopsy showing 10 portal tracts, with only three surviving bile ducts that show degeneration under H&E staining. **(C)** Second liver biopsy showing an increase in the bile duct ratio under H&E staining.

The result showed hemophagocytosis in bone marrow, which met the HLH diagnostic criteria. Intravenous immunoglobulin was thus given from day 61 to day 64.

A repeat liver biopsy was performed on day 127, which revealed intrahepatic cholestasis with marked perivenular bile stasis. Eight portal tracts were observed with seven bile ducts, with six showing degeneration and cell senescence changes. An increase in the bile duct ratio was seen compared to that of the previous study (Figure 3C). Despite the resolution of SJS and VBDS, the patient still developed hypovolemic shock combined with septic shock episodes and died on day 236.

Discussion

Vanishing bile duct syndrome should be suspected in the clinicopathological setting of persistent cholestasis leading to progressive damage and subsequent loss of intrahepatic bile

TABLE 1 Drug-induced Vanishing Bile Duct Syndrome (VBDS) associated with Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).

Case No.	Authors	Age/Sex	Underlying disease	Culprit drug	Interval between drug intake and VBDS	Skin lesion	Treatment	Outcome
1.	Srivastava et al. (8)	9 y/ F	no known history	ibuprofen	10 days	SJS	UDCA, corticosteroids, tacrolimus	Persistence of jaundice >4 months after onset, patient referred for liver transplantation
2.	Garcia et al. (9)	4 y/ M	mental retardation, cerebral palsy, seizures	carbamazepine	4 months	SJS	UDCA, corticosteroids, tacrolimus	Complete clinical and biochemical recovery within 6 weeks
3.	Taghian et al. (10)	10 y/ F	nickel contact dermatitis, tonsillectomy	ibuprofen	12 days	SJS	UDCA, rifampicin, antihistamine, corticosteroids	Complete clinical and biochemical recovery within 7 months
4.	Karnsakul et al. (11)	7 y/ F	no known history	trimethoprim-sulfamethazole	3 weeks	TEN	corticosteroids, cyclosporin	Persistence of jaundice >10 months after onset, patient awaits liver transplantation
5.	Okan et al. (12)	26 y/ F	no known history	ciprofloxacin	2 weeks	SJS	UDCA, corticosteroids, tacrolimus	Complete clinical and biochemical recovery within 10 months
6.	Juricic et al. (13)	62 y/ F	no known history	azithromycin	1 month	SJS	UDCA, corticosteroids, antihistamine	Persistence of jaundice >7 months after onset, patient received liver transplantation
7.	Kim et al. (14)	7 mo/ F	no known history	ibuprofen	8 days	TEN	UDCA	Complete clinical and biochemical recovery within 4 months
8.	White et al. (15)	6 y/ M	asthma	cefdinir acetaminophen	1 week	SJS	UDCA, corticosteroids, rifampin, plasmapheresis, infliximab	Deceased secondary to respiratory failure
9.	Harimoto et al. (16)	40 y/ F	no known history	acetaminophen	NA	SJS	NA	Persistence of jaundice without specified time range, patient received liver transplantation
10.	Basturk et al. (17)	7 y/ M	no known history	ibuprofen	NA	TEN	UDCA, corticosteroids	Complete clinical and biochemical recovery within 8 months
11.	Momen et al. (18)	52 y/ F	GERD	cephalexin	NA	TEN	NA	Persistence of jaundice >5 months after onset, patient received liver transplantation
12.	Li et al. (19)	6 y/ M	no known history	amoxicillin naproxen	NA	SJS	UDCA, corticosteroids, plasma exchange, traditional Chinese medicine (Pien Tze Huang)	Complete clinical and biochemical recovery within 5 months
13.	Bak et al. (20)	29 y/ F	no known history	pelubiprofen	NA	SJS	corticosteroids	Persistence of jaundice >14 months after onset, patient awaits liver transplantation
14.	Massari et al. (21)	51 y/ F	no known history	ketoprofen	14 days	TEN	corticosteroids, IVIG	Persistence of jaundice >7 months after onset, patient received liver transplantation
15.	Present case	42 y/ M	HCV (resolved)	diclofenac	14 days	SJS	corticosteroids, mycophenolate, mofetil IVIG	Deceased secondary to hypovolemic shock and septic shock.

GERD, gastro-esophageal reflux disorder; HCV, hepatitis C virus; UDCA, ursodeoxycholic acid; IVIG, intravenous immunoglobulin; NA, not available.

10.3389/fmed.2022.975754

ducts despite the removal of the offending agent after ruling out other ductopenic diseases (1). Proposed mechanisms of action include direct injury to cholangiocytes after bile excretion, T cell-mediated hypersensitivity reaction resulting in attack against cholangiocytes, and increased exposure to toxic bile salts due to impaired protective defenses of the epithelium. Treatment options remain limited to discontinuation of the offending drug, with possible benefits of ursodeoxycholic acid or corticosteroids when immunoallergic causes are suspected (1).

In our case, which NSAID medication was the exact culprit could not be fully determined due to the prescription of multiple drugs close together. The calculated ALDEN score showed diclofenac as the most likely offending agent, with a score of 3 (4). In reviewing the patient's clinical course, improvement of VBDS could be assumed when combining clinical clues of initially significant decrease in liver enzymes and bilirubin levels after steroid treatment and the repeat liver biopsy on day 127, which showed ductopenia in recovery. However, the patient's general condition further deteriorated, which may partly be attributed to the immunosuppressive effects of steroids and mycophenolate mofetil resulting in CMV and opportunistic infections (5). In addition, steroid-induced poor wound healing may partially account for massive blood passage from resection wounds in the intestine (6).

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive disorder induced by uninhibited activation of macrophages, NK cells, and cytotoxic T lymphocytes, which leads to immune-mediated multi-organ injuries. Clinical and laboratory presentations may vary and include fever, splenomegaly, cytopenia in two or more lineages, hypertriglyceridemia, hyperferritinemia, hemophagocytosis in biopsies, and diminished NK cell activity (3). Epidermal necrolysis (EN) is a lethal mucocutaneous reaction that is mostly medication-induced. EN is further classified as SJS, SJS-TEN overlap, and TEN according to the percentage of detached areas on the skin (7). Due to the similarities between the prodromal phase of EN and infection, the potential viral and bacterial infections should be examined alongside the patient's precise clinical and medication history before the EN diagnosis is finalized. In our case, the patient presented with SJS and VBDS with subsequent development of HLH. T cell-mediated hypersensitivity reaction plays a shared role in the three diseases (1–3), indicating the possible fatality resulting from the hyperimmune response.

To the best of our knowledge, this is the fifteenth report of VBDS associated with SJS or TEN (Table 1). The prognoses varied greatly, with two patients succumbing to death during hospital treatment (15), seven patients requiring liver transplantation (8, 11, 13, 16, 18, 20, 21), and the remaining six patients showing clinical resolution (9, 10, 12, 14, 17, 19). Further studies are necessary to identify the possible risk factors, prognostic indicators, and the standard of care for VBDS with SJS or TEN.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

W-CL analyzed the clinical relevant data and drafted the manuscript. T-SH aided in the data collection and edited the manuscript. C-YC provided the resources, supervised the study, edited, and reviewed the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.975754/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 28 October 2022
DOI 10.3389/fmed.2022.1041492

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 11 September 2022
ACCEPTED 04 October 2022
PUBLISHED 28 October 2022

CITATION
Otsuka H, Fukumoto T, Oka M and Nishigori C (2022) Case report: Severe non-pigmenting fixed drug eruption showing general symptoms caused by chondroitin sulfate sodium. *Front. Med.* 9:1041492. doi: 10.3389/fmed.2022.1041492

Case report: Severe non-pigmenting fixed drug eruption showing general symptoms caused by chondroitin sulfate sodium

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Non-pigmenting fixed drug eruption (NPFDE) is a subtype of fixed drug eruption (FDE) in which repeated eruptions occur at the same site. Clinically, NPFDE disappears without pigmentation changes; however, it sometimes causes fever or arthralgia. Its histopathological characteristics reportedly include infiltrations of CD8-positive T cells with a paucity of melanocytes as compared to FDE. We present the first case of severe NPFDE exhibiting general symptoms caused by chondroitin sulfate sodium. The patient was a 44-year-old man. Intravenous injection of chondroitin sulfate sodium caused erythema in the affected area. A histopathological examination of the biopsy tissue revealed infiltration of CD3-positive lymphocytes (both CD4-positive and CD8-positive lymphocytes) into the epidermis, minimal liquefaction degeneration in the basal layer of the epidermis, and few dermal melanophages, which may be responsible for non-pigmentation.

KEYWORDS

non-pigmenting fixed drug eruption, general symptoms, chondroitin sulfate sodium, histopathological examination, melanophages

Non-pigmenting fixed drug eruption (NPFDE) is a rare subtype of fixed drug eruption (FDE) characterized by repeated eruptions occurring at the same site (1). Clinically, NPFDE resolves without pigmentation changes; however, it sometimes causes fever or arthralgia (1, 2). Herein, we present a case of severe NPFDE exhibiting general symptoms caused by chondroitin sulfate sodium. To the best of our knowledge, this is the first case of its kind. Moreover, the histopathological examination of the biopsy specimen from our patient showed NPFDE characteristics that possibly caused the clinical phenotype (1, 3, 4).

The patient was a 44-year-old male involved in a traffic accident that resulted in neck pain. He was treated with an intravenous injection of a mixed agent containing

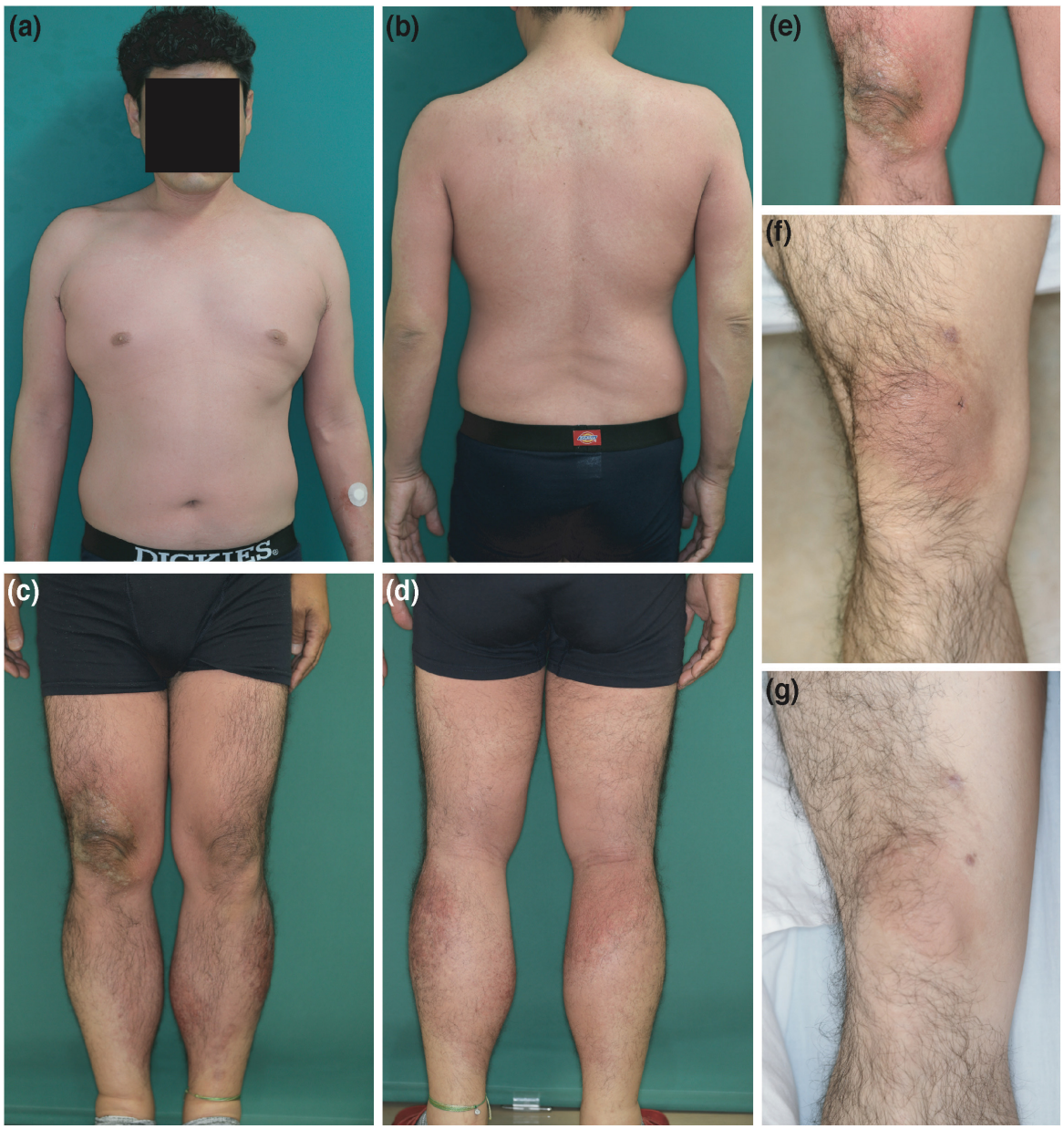

FIGURE 1
Clinical features. **(a–e)** Erythematous skin eruptions that first appeared on the right knee and subsequently spread all over the body, except for the upper back and the ends of the extremities, at the first consultation. **(f)** Clearly demarcated erythema on the right knee only after the intravenous injection (as is) with the mixed agent containing chondroitin sulfate sodium and sodium salicylate. **(g)** Clearly demarcated erythema on the right knee after intravenous injection with chondroitin sulfate sodium (as is).

chondroitin sulfate sodium and sodium salicylate three times every second day. Four days after three courses of treatment (total chondroitin sulfate sodium = 600 mg), the patient developed erythematous skin eruptions with clear boundaries, which started on the right knee and subsequently spread all over the body except for the upper back and the ends of the extremities. Additionally, the patient had fever and arthralgia (Figures 1a–e).

The histopathological examination revealed infiltration of CD3-positive lymphocytes (both CD4-positive and CD8-positive lymphocytes) into the epidermis. In addition, there was minimal liquefaction degeneration in the basal layer of the epidermis and few dermal melanophages (Figures 2a–e). Furthermore, Melan-A staining did not reveal a paucity of melanocytes, and Fontana-Masson staining did not show increased staining (Figures 2f,h). Additionally,

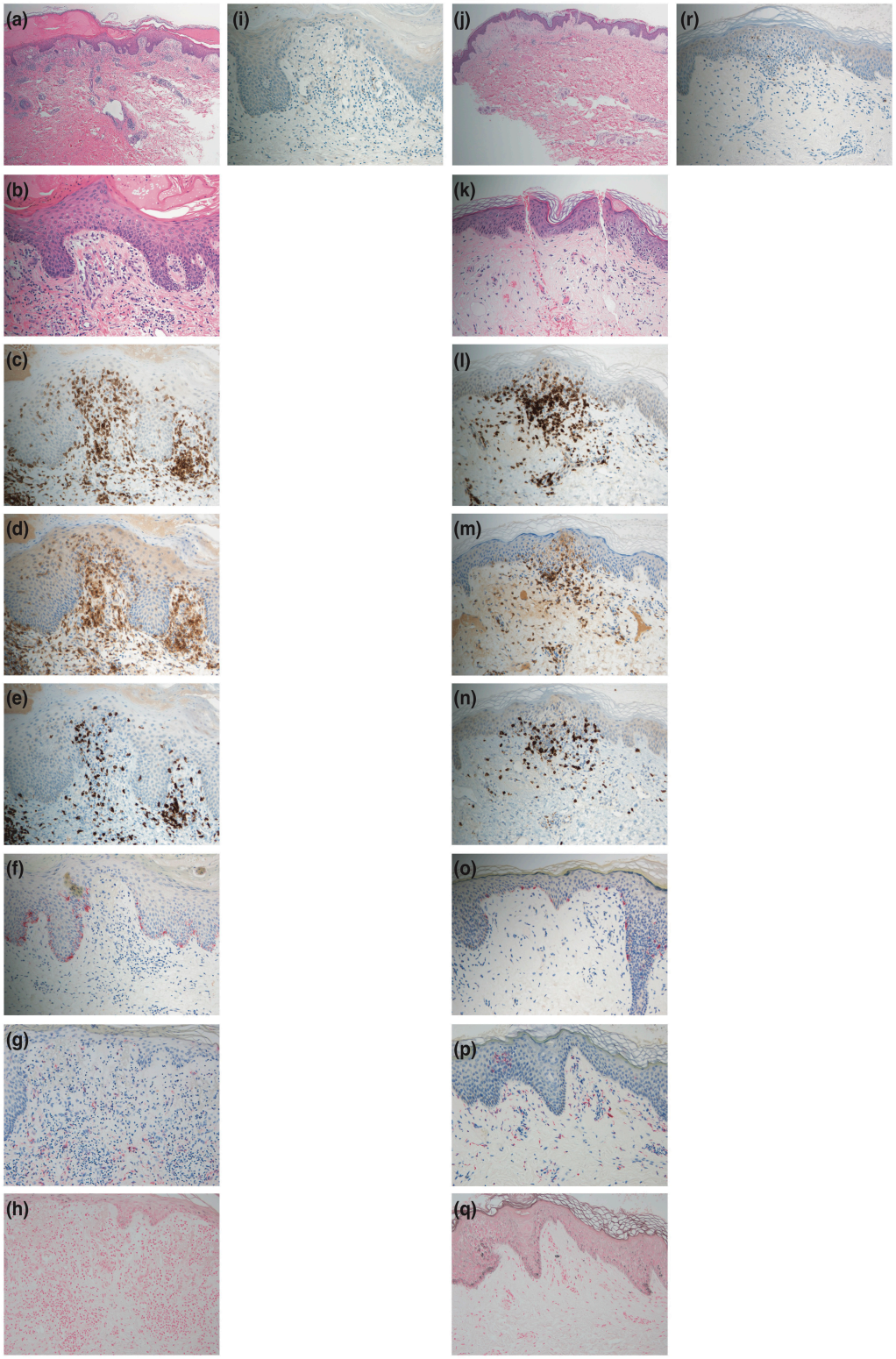

FIGURE 2
Histopathological features. **(a,b)** Hematoxylin-eosin staining of a skin biopsy specimen from the right knee at the first consultation showing minimal liquefaction degeneration in the basal layer of the epidermis. Also, lymphocytes and eosinophils are observed around the blood vessels of the dermis [panel **(a)** × 40, panel **(b)** × 200]. **(c)** CD3 staining showing positive results in the cell infiltrations (× 200). **(d)** CD4 staining showing positive results in the cell infiltrations (× 200). **(e)** CD8 staining showing positive results in the cell infiltrations (× 200). **(f)** Melan-A staining showing positive results in melanocytes (× 200). **(g)** Few melanophages in the dermis with CD68-positive staining (× 200).

(Continued)

FIGURE 2 (Continued)
(h) Fontana-Masson staining showing no increased staining (× 200). **(i)** Myeloperoxidase staining showing negative results in the cell infiltrations (× 200). **(j,k)** Hematoxylin-eosin staining of a skin biopsy specimen from the right knee after the challenge test by intravenous injection (as is) with the mixed agent containing chondroitin sulfate sodium and sodium salicylate showing minimal liquefaction degeneration in the basal layer of the epidermis. Also, lymphocytes and eosinophils are observed around the blood vessels of the dermis [panel **(j)** × 40, panel **(k)** × 200)]. **(l)** CD3 staining showing positive results in the cell infiltrations (× 200). **(m)** CD4 staining showing positive results in the cell infiltrations (× 200). **(n)** CD8 staining showing positive results in the cell infiltrations (× 200). **(o)** Melan-A staining showing positive results in melanocytes (× 200). **(p)** Few melanophages in the dermis with CD68-positive staining (× 200). **(q)** Fontana-Masson staining showing no increased staining (× 200). **(r)** Myeloperoxidase staining showing negative results in the cell infiltrations (× 200).

myeloperoxidase staining of the cell infiltrations was negative (**Figure 2i**), and eosinophils were observed around the blood vessels in the dermis (**Figures 2a,b**).

The mixed agent treatment (containing chondroitin sulfate sodium and sodium salicylate) was discontinued, and the patient received topical clobetasol propionate and an oral antihistamine, which alleviated his skin eruptions within a week, leaving no pigmentation.

The patient provided written informed consent to undergo further testing to isolate the cause of the erythema after we excluded viral etiologies. A patch test was performed on the patient's upper back (unaffected skin) and the right knee (affected skin), where the erythema first developed, to check for any reaction to the mixed agent containing chondroitin sulfate sodium and sodium salicylate. Both sites were negative. Additionally, the results for the prick and intracutaneous tests at the left forearm were negative. While intravenous injection (1%; 2 mg of chondroitin sulfate sodium) with the mixed agent elicited a negative response, the intravenous injection (as is; 200 mg of chondroitin sulfate sodium) with the mixed agent led to erythema recurrence without pigmentation in the right knee alone, where marked erythema was initially noted (**Figure 1f**) after 24 h, and without fever and arthralgia. Histopathological examination of the erythematous lesion revealed similar characteristics to those noted previously (**Figures 2j–r**). Consistent with the clinical images of the knee, histopathological examinations showed hyperkeratosis, potentially caused by mechanical stress.

Subsequently, the effects of chondroitin sulfate sodium and sodium salicylate were independently examined. The results of patch and prick tests on the upper back and right knee with the individual components were negative. No changes occurred after intravenous injections with sodium salicylate (1% and as is) and chondroitin sulfate sodium (1%). However, intravenous injection with chondroitin sulfate sodium (as is) caused erythema recurrence without pigmentation in the right knee alone, similar to the response of the mixed agent (as is) (**Figure 1g**). Therefore, the patient was diagnosed with NPFDE caused by chondroitin sulfate sodium.

This report emphasizes two critical learning points. First, this was the first case of severe NPFDE exhibiting general symptoms caused by chondroitin sulfate sodium. Second, the NPFDE lesion was characterized by infiltration comprising of CD4-positive and CD8-positive T cells, minimal liquefaction degeneration in the basal layer of the epidermis, and few dermal melanophages. A previous study reported increased CD8-positive T cells in an NPFDE lesion (2); however, in our patient, both CD4- and CD8-positive T cells were present. Therefore, we hypothesized that these CD4-positive T cells might be regulatory T cells, which predominantly infiltrate the lesion, resulting in lesser liquefaction degeneration and a rapid resolution of inflammation. However, further studies are needed to confirm this.

Fixed drug eruption (FDE) is normally characterized by liquefaction degeneration in the basal layer and dermal melanophages, leading to clinical pigmentation (5). However, in our patient, the liquefaction degeneration in the basal layer was minimal, and the number of melanophages in the dermis was limited, despite excessive intraepidermal inflammatory cell infiltration. This can be attributed to the absence of melanophages in the dermis, due to minimal liquefaction degeneration, and the presence of a majority of the CD4-positive and CD8-positive T cells in the epidermis and not the basal layer. As previously reported, these factors may be responsible for the lack of pigmentation (5).

Our report has several limitations. First, our observation is based on a single case. Second, our patient did not react to the patch test, even in the affected area. Andrade et al. (4) have recommended performing the patch test a few weeks to a few months after resolution due to a potential refractory period, which may explain this result (4, 6). Additionally, they reported that less than half the patch tests were reactive, even in the affected area because of some potential reasons such as penetration rate and molecular size of drugs, features of vehicles, and lack of systemic transformation for immune response activation (4, 6). In these cases, oral challenge and intravenous injection of culprit drugs, epidermal thinning (e.g., tape stripping), increased concentration of drugs, and prolonged duration of occlusion may be useful (4, 6).

Nonetheless, we report a rare, severe case of NPFDE showing general symptoms, characterized by minimal liquefaction degeneration with few dermal melanophages and increased CD4-positive and CD8-positive T cells. Chondroitin sulfate sodium is a dietary supplement, commonly used to treat osteoarthritis (7). Therefore, this report may serve as a cautionary case, urging clinicians to consider the risk of

NPFDE in any case of erythema following chondroitin sulfate sodium administration.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The patient has given informed consent for the publication of this report.

Author contributions

HO and TF designed the study and contributed to data collection. All authors wrote the manuscript, read, and approved the final manuscript.

Funding

This work was supported by KOSÉ Cosmetology Research Foundation (TF) and Kinoshita memorial enterprise subsidy (TF).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Case Report
PUBLISHED 17 November 2022
DOI 10.3389/fmed.2022.1052145

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 23 September 2022
ACCEPTED 26 October 2022
PUBLISHED 17 November 2022

CITATION
Schauer F, Casetti F and Kiritsi D (2022) Case report: Minimal manifestations of mucous membrane pemphigoid in a young adult. *Front. Med.* 9:1052145. doi: 10.3389/fmed.2022.1052145

Case report: Minimal manifestations of mucous membrane pemphigoid in a young adult

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A male patient presented to our department at the age of 23 suffering from recurrent painful erosions in the urethral outlet area. In closer clinical examination gingival erosions, primarily around the teeth were identified as well. Indirect immunofluorescence on salt split skin with epidermal IgG deposition and positive anti-BP230 IgG ELISA diagnostics hinted toward the presence of mucous membrane pemphigoid (MMP). Direct immunofluorescence from oral mucosa confirmed the diagnosis. MMP in young adulthood is an underdiagnosed disease and latency of diagnosis was around 4 years in our case. Treatment with systemic glucocorticosteroids and dapsone led to clinical remission, prohibiting the development of MMP manifestations in further organs and complications associated with the disease, e.g., scar formation and miction problems.

KEYWORDS

blistering disorder, skin fragility, urethral erosion, autoimmune disease, hemidesmosome, BP230

Introduction

Mucous membrane pemphigoid (MMP) is an autoantibody-mediated subepidermal blistering disease with predominant involvement of mucous membranes and tendency of scarring (1). The scarring can interfere with the patients' normal functions, e.g., vision, food intake, miction, and sexual intercourse, thus have a serious impact for their quality of life (2). Larynx involvement might even be fatal due to breathing impairment (3). The diagnosis is based on clinical findings and the detection of autoantibodies against known autoantigens at the basement membrane, primarily BP180, BP230, laminin 332, and collagen VII (4). Direct and/or indirect immunofluorescence diagnostics, as well as ELISA for the specific proteins and immunoblotting are essential for correct diagnosis (4). We here present a male patient with only few erosions on his gingiva and urethra and minimal inflammatory signs of the disease, who was diagnosed having an MMP and responded to immunosuppressive treatment.

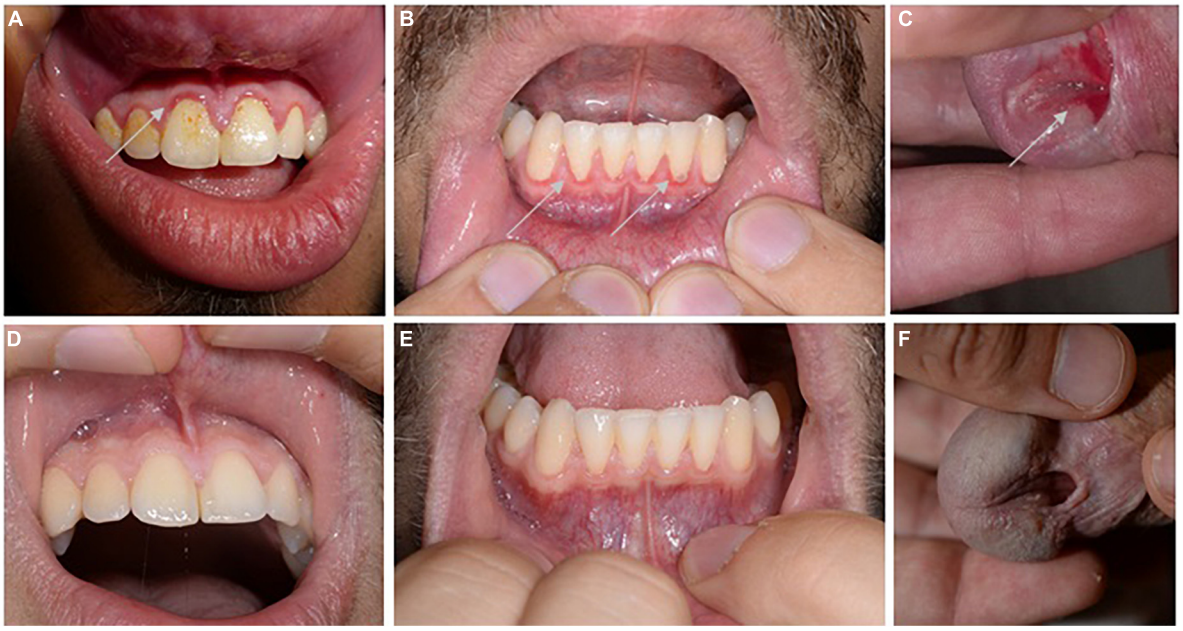

FIGURE 1
Clinical picture. Discrete swelling and erosions (highlighted by arrows) around the gingival fringes of the upper **(A)** and lower tooth space **(B)**, as well as a painful ulcer at the urethral entrance were identified at initial presentation **(C)**. Inconspicuous mucosal findings of the upper gingiva **(D)** and lower gingiva **(E)** and urethral outlet **(F)** followed initiation of therapy with prednisolone combined with dapsone.

Case report

A 23-year-old male patient from middle Europe suffered from recurrent, painful erosions in the urethral outlet area since around 4 years. Due to congenital hypospadias in the urethral area, he was regularly examined by urologists. The persistence of the mucosal lesions resulted in referral to our Dermatology department. Clinical examination showed an ulcer on the urethral outlet area, but also few erosions on the gingiva, which mimicked a mild gingivitis (**Figure 1**). He was not hampered by the gingival lesions in his everyday life. He was otherwise healthy, without any medication. Sexually transmitted disorders had been ruled out.

We initiated specific diagnostics for autoimmune blistering disorders. The indirect immunofluorescence on salt split skin showed epidermal IgG reactivity at blister roof, compatible with an active pemphigoid disorder (**Figure 2A**). In addition, an isolated positive BP230 ELISA at 85 U/ml (cut of > 9 U/ml) was identified, while NC16A BP180 ELISA was negative (MBL, Nagoya, Japan). The subsequently performed analysis from a biopsy of unaffected buccal mucosa revealed IgG and C3 deposition at the dermal-epidermal junction in the direct immunofluorescence (**Figures 2B–D**). Immunoblotting analysis using human epidermal extract as substrate showed IgG immunoreactivity with BP230 and slightly also collagen VII (**Figure 2F**). IgA autoantibodies did not react in any analysis. Histological examination taken from buccal mucosa yielded a hyperplastic, non-keratinizing, mucosal epithelium without cleavage (**Figure 2E**). No inflammatory infiltrate was detectable in the dermis nor evidence for PAS-positive fungal elements were identified. The patient was treated with oral prednisolone 0.3 mg/kg body weight and oral dapsone 50 mg/day (0.8 mg/kg body weight). Lesions of the patients healed with topical tacrolimus 0.1% ointment for the urethral area and triamcinolone acetonide 0.1% cream for the gingiva after 8 weeks.

Discussion

Mucous membrane pemphigoid (MMP) is a chronic and usually blistering disorder with about 2/million inhabitants/year being diagnosed in central Europe (5). In general, MMP can affect multiple mucosal sites, but oral mucosa is most frequently involved, followed by ocular, anogenital, nasopharyngeal, laryngeal, and esophageal sides (5, 6). It is considered a disease of the elderly with disease onset typically within the 6th decade of life (7). In young adulthood it is rarely described and sometimes associated with trauma (8). On the other hand, vulvar or urethral MMP has been described in children as well, while the genital area appears to be more commonly affected than other mucosal surfaces at young age (9). Altogether, less than 20 cases of isolated genital MMP have been reported in the literature, notably with either children or geriatric patients being affected

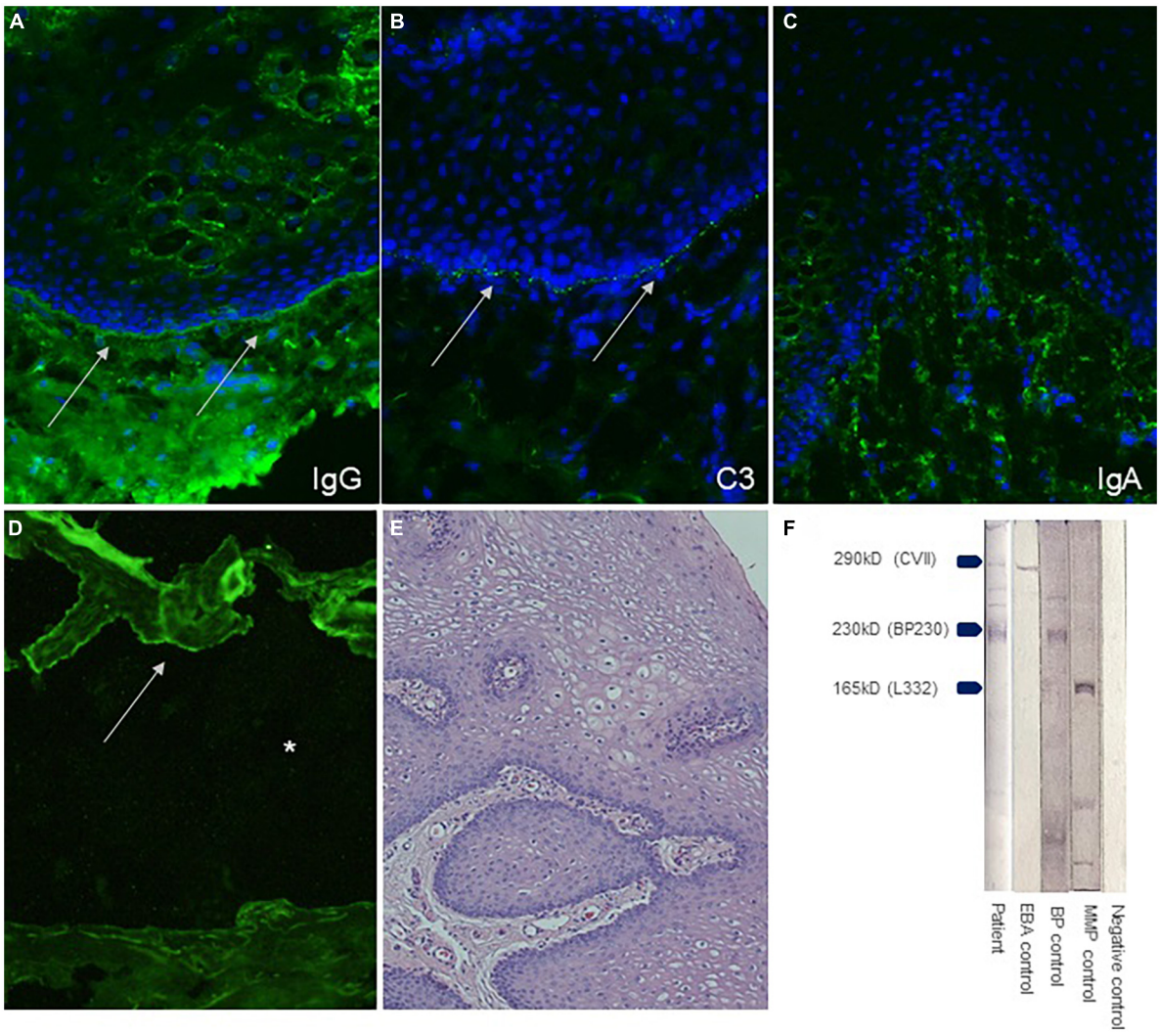

FIGURE 2
Direct immunfluorescence (DIF) of buccal mucosa shows linear IgG and C3 depositions at basement membrane zone, each indicated by arrows **(A,B)**. DIF found no reactivity for IgA **(C)**. Indirect immunofluorescence on 1M split human skin using patient's serum shows epidermal staining of IgG **(D)**. Histopathology of buccal mucosa of the patient (hematoxylin-eosin stain, 200x magnification) **(E)**. Immunoblot analysis revealed IgG autoantibodies against BP230 and slightly also against collagen VII **(F)**.

(10–13). The fact that more cases are being reported in recent years is likely due to increased awareness and easier access to serological testing (10–12). The latency to diagnosis in our case was approximately 4 years, which is to be expected for such mild disease manifestations. Hopefully, the time between disease manifestation and diagnosis can be shortened as more cases are presented.

The gingival lesions as in our case could be misinterpreted as periodontitis. Additionally, our patient had suffered with congenital hypospadias with complicating development of urethral fistula after surgical correction 18 years ago. It remains unclear whether the latter may have already been part of the autoimmune bullous disease activity or actually the trauma initiated the development of autoantigens.

According to literature NC16A BP180 is the most frequent autoantigen in MMP patients followed by reactivity against the LAD-1 ectodomain and laminin 332 (14). Reactivity against BP230 as in our patients is only found in a minority of patients (14–16), while their pathogenetical relevance is disputed, since BP230 is an intracellular antigen (17). Nonetheless, we here present a case with genital MMP involvement due to primarily BP230 autoantibodies, with no similar cases described so far. Serological tests are frequently negative at initial MMP disease stages, thus repeated sampling is required when clinical suspicion for MMP exists (18).

Mucous membrane pemphigoid (MMP) is feared for its treatment refractory course. Our patient responded well to the combination of low dose prednisolone with dapsone, but

relapsed mildly when prednisolone was tapered. Instead of dapsone, classical immunosuppressants as mycophenolate or azathioprin can be employed, while rituximab is considered an off-label ultima ratio, especially in severely scarring courses (19–21). Finally, other approaches with intravenous immunoglobulins or omalizumab have been reported to be useful as well (22, 23).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Human Ethics Committee University of Freiburg (reference no. 235/15). Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FS, FC, and DK had full access to all of the data in the study. FS and DK took responsibility for the integrity of the data and the accuracy of data analysis. All authors read, revised, and approved the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TYPE Case Report
PUBLISHED 18 November 2022
DOI 10.3389/fmed.2022.1009135

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 01 August 2022
ACCEPTED 01 November 2022
PUBLISHED 18 November 2022

CITATION
Nie S, Li K, Gao C, Yin N, Chen Z and Wu Z (2022) Eyebrow tattoo-associated sarcoidosis: A case report.
Front. Med. 9:1009135.
doi: 10.3389/fmed.2022.1009135

Eyebrow tattoo-associated sarcoidosis: A case report

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Cutaneous sarcoidosis can manifest after doing a permanent makeup (PMU), such as tattooed eyebrows. A 41-year-old Chinese woman, with a tattoo in the eyebrows, developed yellow–brown plaques in her eyebrows for several months. A dermatopathological examination revealed non-caseating granulomas consistent with cutaneous sarcoidosis. For months, topical corticosteroids were applied, which showed little effect. Furthermore, a physical evaluation of the patient revealed no apparent involvement of other body organs except bilateral hilar lymphadenopathy with few diffuse reticulonodular opacities. On the basis of fully informed consent, the patient agreed to a 6-month initial follow-up to avoid unnecessary PMU.

KEYWORDS

sarcoidosis, permanent makeup, tattoo, granulomas, eyebrow

Introduction

Sarcoidosis is an inflammatory granulomatous disease characterized by non-caseating epithelioid granulomas in multiple organs, for which the etiology and pathophysiology are unidentified. In roughly a quarter of cases, cutaneous sarcoidosis is the initial manifestation of the disease (1, 2). Over the past decade, studies have documented on reporting granuloma nodosum on tattoos or permanent makeup (PMU) (3–5). The popularity of tattoos and PMU is on the rise. Though tattoos are generally considered harmless, nonetheless, adverse reactions, namely, allergic reactions, infections, or (systemic) autoimmune diseases can occur. Furthermore, PMU can be a sarcoidosis trigger, and the prevalence of sarcoidosis may increase as its popularity grows. Granuloma and nodular tattoo reactions can be the initial and occasionally the only skin manifestations of systemic sarcoidosis (6). Specifically, we reported a 41-year-old Chinese woman who developed yellow–brown plaques in her eyebrows months after receiving a tattoo in the same location.

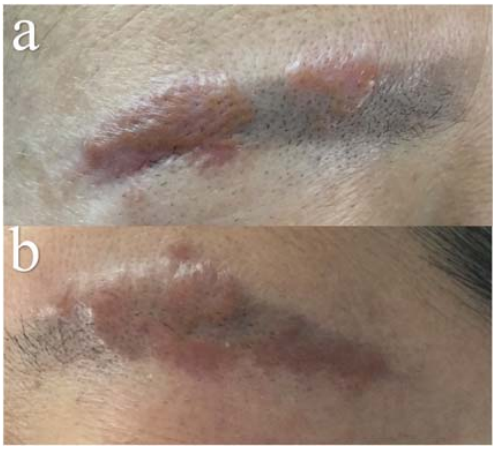

FIGURE 1
Clinical manifestation. Reddish and yellow–brown plaque within the areas of previous black–brown eyebrow tattoos [Right **(a)** and Left **(b)**].

Case presentation

A 41-year-old Chinese woman presented to our clinics with a slowly enlarged rash on the bilateral eyebrows, which had developed for several months without itching or tenderness. The patient exhibited no other symptoms, such as coughing.

On physical examination, extensive black–brown tattoos on both eyebrows were observed. There were grouped reddish and yellow–brown infiltrative papules, some of which coalesced into plaques scattered over the tattoo (**Figures 1a,b**). There were no scales or ulcers found.

The patient disclosed that she had tattooed her eyebrows 3 months before the rash appeared. She was treated with topical clobetasol propionate cream for over 2 months, nevertheless, there was no notable improvement. She denied any history of trauma, sojourn, or contact with animals. Prior to her dermatology clinic visit, she had no other sarcoidosis-related signs or symptoms. No sarcoidosis-related family history was reported.

The results of laboratory tests such as serum angiotensin-converting enzyme (ACE) levels and T-spot were within normal limits (**Table 1**). Enhanced computed tomography (CT) of the chest with contrast demonstrated a few diffuse reticulonodular opacities in the bilateral lower lobe, bilateral hilar lymph nodes enlargement, and in the posterior segment of the right upper lobe are some small ground glass nodules (**Figures 2a,b**). The patient declined additional invasive diagnostic procedures, such as bronchoscopy/BAL or EBUS for lymphadenopathy.

A biopsy of yellow–brown plaque within the eyebrow tattoo indicated non-caseating granulomas throughout the dermis consistent with a diagnosis of cutaneous sarcoidosis (**Figures 3A,B**). Grocott–Gomori methylamine silver stain acid-fast bacilli were negative. Throughout the granuloma, black tattoo pigment was discovered (the arrows in **Figures 3A,B**).

Tattoo-associated sarcoidosis was diagnosed based on the clinical manifestation of yellow–brown plaque and histopathological findings of non-caseating granulomas at the tattoo site. Lung involvement is considered stage I (1). Since the patient's symptoms did not enhance following topical steroids, we have decided to follow up with patients every 6 months to avoid unnecessary tattoos (1).

Discussion

Approximately, 10–20% of the global population is tattooed (7). Notwithstanding, due to the influence of traditional culture in China, tattoos are predominantly employed for PMU, especially eyebrow tattoos. Thus, the negative effects of eyebrow makeup are increasing in China. Uncertain is the precise mechanism of sarcoidosis in eyebrow makeup. It has been reported that chronic and minimal ink exposure may stimulate the granulomatous response and may eventually lead to the development of sarcoidosis in genetically susceptible individuals (8). Our patient showed normal ACE levels, a known sarcoidosis marker (1). However, an elevated ACE level is not diagnostic and a normal level does not rule out sarcoidosis. Surgery, corticosteroids (systemic, topical, intralesional), minocycline, and other treatments are used to treat sarcoidosis, but results are inconsistent (1, 9). The clinical manifestations, natural history, and prognosis of sarcoidosis vary widely, with spontaneous regression, or ebb and flow of disease fluctuations, or in response to therapy. Approximately two-thirds of patients experience spontaneous remission within 12–36 months, whereas 10–30% of patients have chronic or progressive disease (10, 11). Severe extra-pulmonary involvement (mainly heart, nervous system, and liver) has been reported in approximately 4–7% of patients (1). When there is pulmonary fibrosis, it can be life-threatening, with pulmonary hypertension, or cardiac involvement (12, 13). Given that all patients with cutaneous sarcoidosis are likely to develop systemic involvement, it is necessary to assess the risks of morphologically related systemic involvement of cutaneous sarcoidosis (14). Macules and papules with the least correlation with systemic disorders, and typically have a favorable prognosis. Annular lesions or

TABLE 1 The details about routine investigations.

Item	Results	Reference ranges
CBC	7.11×10^9/L	$3.69–9.16 \times 10^9$/L
ESR	9mm/H	0–20 mm/H
CRP	1.2mg/L	0–10 mg/L
ACE	40.07U/L	12–68 U/L
T-SPOT	Neg	Neg

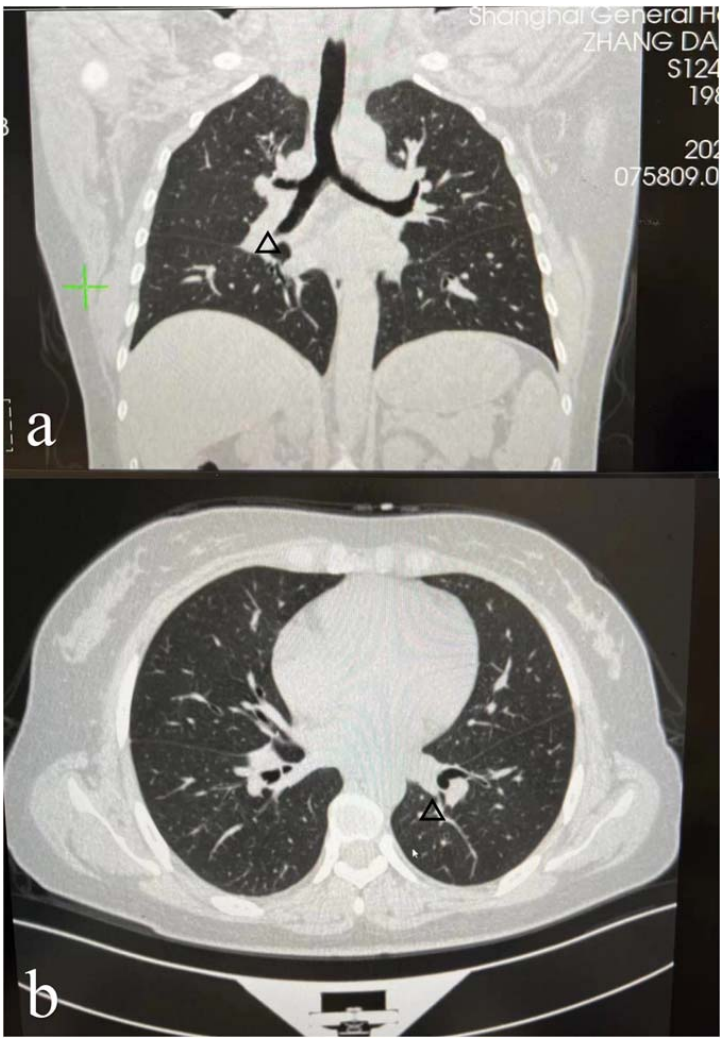

FIGURE 2
Enhanced computed tomography (CT) of the chest with contrast demonstrated a few diffuse reticulonodular opacities in the bilateral lower lobe, bilateral hilar lymph nodes enlargement [the arrows in panels **(a,b)**], and in the posterior segment of the right upper lobe are some small ground glass nodules.

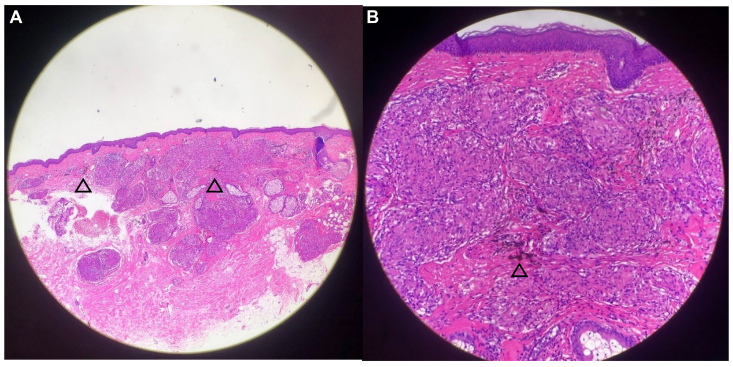

FIGURE 3
Histopathological examination demonstrated non-caseating granulomas with pigment granules and mild lymphocytic infiltration. Black tattoo pigment is seen throughout the granuloma [the arrows in panels **(A,B)**] [Hematoxylin–Eosin, original magnification ×4 **(A)**, ×20 **(B)**].

plaques have poor prognoses and a higher risk of systemic involvement. Lupus pernio had a more chronic course than plaque sarcoidosis and correlated significantly with upper respiratory tract and bone involvement. In addition, Heerfordt's syndrome always has a poor prognosis (14, 15). After 2 months of topical corticosteroid treatment, our patient did not improve significantly. Considering that approximately two-thirds of patients undergo spontaneous remission within 12–36 months after communicating with the patient, we agreed to follow up on the changes of the condition in the next 6 months with skin and chest CT examination, and avoiding unnecessary PMU was advised.

Our patient had an eyebrow tattoo with the purpose of seeking beauty and yet got the opposite result, and the treatment result was not satisfactory. We are aware that PMU may contain more complementary colors and shape alterations than conventional tattoos. Theoretically, repeated tattooing and reintroduction of foreign material into the skin may activate the immune system (16). Clinicians have begun to recognize and predict potential adverse effects in patients with PMU. Detailed clinical information is essential to deliver appropriate treatment to this patient population (17). These patients might represent subclinical cases or cases predisposed to sarcoidosis later in life and consequently, must be monitored. Limited information is available on PMU complications. Existing research consists primarily of case reports and case series with few original studies, and treatment guidelines are still lacking. Furthermore, there is an urgent need for market oversight and restrictions on tattoo ink, as well as the monitoring of tattoo complications.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

SN: data collection, formal analysis, and writing—original draft. KL, CG, NY, ZC: writing—review and editing. ZW: conceptualization, resources, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 24 November 2022
DOI 10.3389/fmed.2022.1054544

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 26 September 2022
ACCEPTED 08 November 2022
PUBLISHED 24 November 2022

CITATION
Moro F, Ciccone D, Fania L, Mariotti F, Salemme A, Rahimi S, Pallotta S and Di Zenzo G (2022) Case report: A rare case of imiquimod-induced atypical pemphigus vulgaris. *Front. Med.* 9:1054544. doi: 10.3389/fmed.2022.1054544

Case report: A rare case of imiquimod-induced atypical pemphigus vulgaris

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Background: Pemphigus vulgaris is an autoimmune intraepithelial bullous disease involving the skin and the mucous membranes. Imiquimod, a topical therapy for skin basal cell carcinoma, is an amine that induces the production of tumor necrosis factor alfa, interleukin-1 and other cytokines. Pemphigus induced by drugs has been frequently reported, mostly after systemic therapy.

Case presentation: We present the case of a 50-year-old man who developed skin, intraoral, and genital mucosae lesions 3 days after a treatment with Imiquimod for multiple superficial basal cell carcinoma of the trunk. Direct and indirect immunofluorescence results were compatible with the diagnosis of pemphigus vulgaris. Enzyme-linked immunosorbent assay was negative for desmoglein 1 and 3, but interestingly, by immunoblotting on keratinocyte extracts a band of 170 kDa was obtained by IgG. The patient, after interrupting Imiquimod application, started a treatment with prednisolone and in 4 weeks showed a complete remission.

Conclusion: Topical Imiquimod therapy might induce atypical pemphigus vulgaris in some patients.

KEYWORDS

pemphigus vulgaris, imiquimod, adverse events, Dsg1, Dsg3, non-desmoglein antigen

Introduction

Pemphigus vulgaris (PV) is an autoimmune intraepithelial bullous disease involving the skin and the mucous membranes clinically characterized by erosions and flaccid bullae. PV affects patients with a male-to-female ratio of 1:1.8 (age range 50–60 years), with an annual incidence of 2–10 per one million inhabitants in central Europe and 4.2 in the American general population, but it depends on the geographical area and the ethnicity (1, 2). PV is caused by anti-desmoglein 1 (Dsg1) and/or anti-desmoglein 3 (Dsg3) autoantibodies responsible for the loss of adhesion between keratinocytes leading

to acantholysis and intra-epidermal blisters (1). However, several other non-desmoglein autoantibodies have been linked to acantholysis observed in PV and these cases are usually termed atypical pemphigus (2).

Imiquimod (Aldara; 3M Pharmaceuticals, St. Paul, MN, USA) is an imidazoquinolone amine that acts as a ligand of the Toll-like receptor 7 inducing the production of tumor necrosis factor (TNF)-alfa, interleukin (IL)-1, IL-1 antagonists, IL-6, IL-10, IL-12, and additional cytokines including interferon (IFN)-alfa (3).

Imiquimod is used as topical therapy to treat basal cell carcinoma (BCC) with a high histological clearance and good cosmetic outcomes (4).

Pemphigus induced by drugs has rarely been described with pemphigus foliaceus as the most common variant (5). A great variety of drugs have been implicated in the mechanism of acantholysis such as allopurinol and angiotensin-converting-enzyme inhibitors. In most cases the drug implicated was used for systemic therapy (5).

Case description

A 50-year-old Caucasian man presented in January 2017 with papules, nodules and erosive lesions on the skin of the upper trunk, on the lips, oral cavity, pharynx, larynx, and on the genital mucosae. On clinical examination, the skin showed papules, nodules on erythematous base in a seborrheic distribution (**Figure 1A**). The erosions on the lips and mucous membrane lesions were painful (**Figure 1B**). The Nikolsky's sign in our patient was positive. At physical examination no other remarkable sign was detected. The patient suffers from hypertension and a diagnosis of multiple superficial BCCs was set 2 months before. In his family no one else had similar cutaneous symptoms and there is no history of autoimmune diseases.

The patient was being treated with Imiquimod for multiple superficial BCCs for 3 days before the onset of the lesions (**Figure 1C**). The findings of routine laboratory tests, chest radiography and abdominal computed tomography scan were within normal limits (**Figure 2**).

The diagnosis of pemphigus vulgaris was based on the typical clinical and morphological criteria. Histopathological examination showed an intraepidermal acantholytic blister compatible with PV (**Figure 1D**). Direct immunofluorescence (DIF) displayed a weak intercellular deposition of IgG and C3 (**Figure 1E**). Indirect immunofluorescence (IIF) on a monkey esophagus substrate showed epithelial intercellular IgG with a 1:160 titer. Of note, Enzyme-linked immunosorbent assay (ELISA) was negative for both Dsg 1 and 3 (1.6 and 0.8 U/ml, respectively; negative, <14 U/ml; indeterminate, 14 to 20 for Dsg1 and negative < 7 U/ml; indeterminate, 7–20 for Dsg3) (MBL, Nagoya, Japan) instead, a 170 kDa band, obtained by IgG, was seen by immunoblotting (IB) with keratinocyte extracts (**Figure 1F**). The negative results on Dsgs were also confirmed by IB and different commercial Dsg1 and 3 ELISA kits (Euroimmun, Padova, Italia). Since epidermal growth factor receptor (EGFR) presents a molecular weight marker similar to the unknown antigen, we also performed an IB on keratinocyte extracts using an anti-EGFR antibody as control (**Figure 1G**). The results showed that the autoantigen did not comigrate with EGFR. The non-desmoglein autoantigen prompts us to term the case as atypical pemphigus vulgaris. The patient, after interrupting Imiquimod application, started treatment with prednisolone (80 mg iv/day) for 7 days, gradually tapered and finished after 4 weeks, with complete clearing of skin and mucosal lesions. The patient reported no physical or psychological sequelae, and he did not have any problem in returning to his everyday life. After reaching clinical remission without therapy, the patient underwent regular follow-up visits and after 2 years did not develop any relapse (**Figure 2**).

Discussion

To the best of our knowledge, only four patients with pemphigus induced by Imiquimod have been reported. Two patients showed an intercellular IgG deposition by DIF, one was negative by DIF and one patient not tested (6–9). Three patients developed Imiquimod-induced erosions on the application site and only one DIF negative patient developed general bullae distant from the site of application (6). Circulating autoantibodies were tested by IIF in one patient who showed an intercellular staining with antibodies at a titer of 1:200 (7). To our knowledge no study investigated the reactivity to Dsg1 and 3 by ELISA and/or IB.

In the case reported herein the circulating autoantibodies failed to react against Dsg1 and Dsg3 while bound to an unknown keratinocyte antigen of 170 kDa. However, the anti-keratinocyte autoimmune response is demonstrated by intercellular labeling due to IgG deposition and circulating IgG which could provoke lesions distant from the site of application of Imiquimod. In this context, Imiquimod therapy has been reported to induce several autoimmune conditions such as psoriasis, vitiligo and exacerbations of myasthenia gravis (10).

A putative pemphigus autoantigen of 170 kDa could be EGFR. Several studies demonstrated that EGFR is involved in the cellular stress response that could lead to blister formation (2). Thus, its role in PV pathogenesis and the molecular weight similar to the unknown antigen prompt us to verify whether EGFR was an autoantibody target without success. Another possible autoantigen of 170 kDa could be alpha-2-macroglobulin-like-1 (A2ML1), a broad range protease inhibitor frequently targeted by paraneoplastic pemphigus autoantibodies. However, the reducing condition used in IB experiments did not allow to detect A2ML1 that is usually

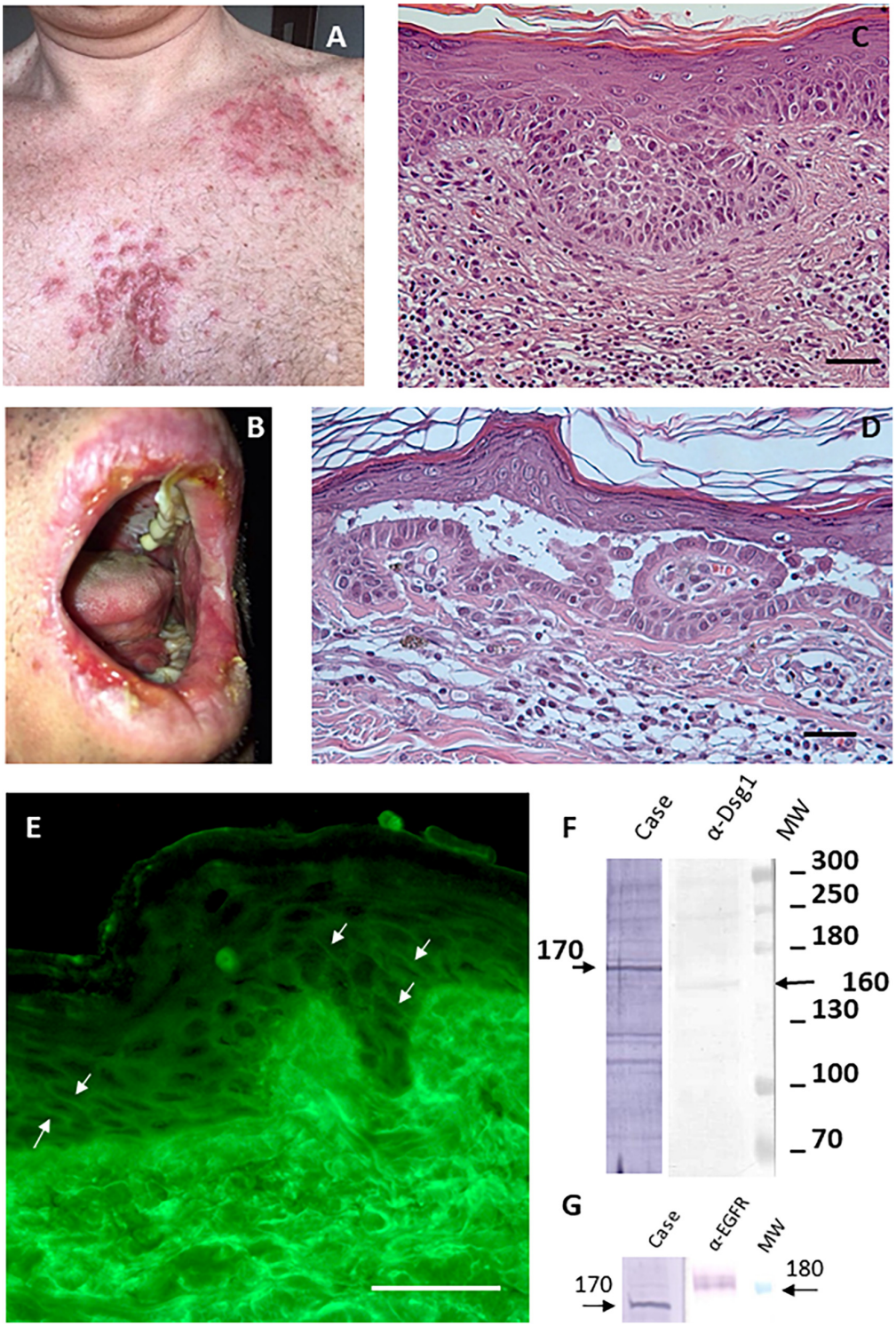

FIGURE 1
Imiquimod-induced pemphigus vulgaris. **(A)** Papules and nodules on erythematous base in seborrheic distribution. **(B)** Painful erosions on the lips. **(C)** Diagnosis of superficial variant of basal cell carcinoma made through histological analysis (scale bar: 100 μm). **(D)** Histological examination shows intraepidermal acantholytic blister with a suprabasal cleavage plane compatible with atypical pemphigus vulgaris (scale bar: 100 μm). **(E)** Direct immunofluorescence displayed a weak intercellular deposition of IgG (scale bar: 100 μm). **(F)** By IB on keratinocyte extracts a band of 170 kDa was obtained by IgG (case), the molecular weight marker and anti-Dsg1 control antibody confirm that reactivity involves an unknown antigen of 170 kDa. **(G)** IB on keratinocyte extracts shows that the 170 kDa band does not correspond to EGFR detected by a specific α-EGFR polyclonal antibody.

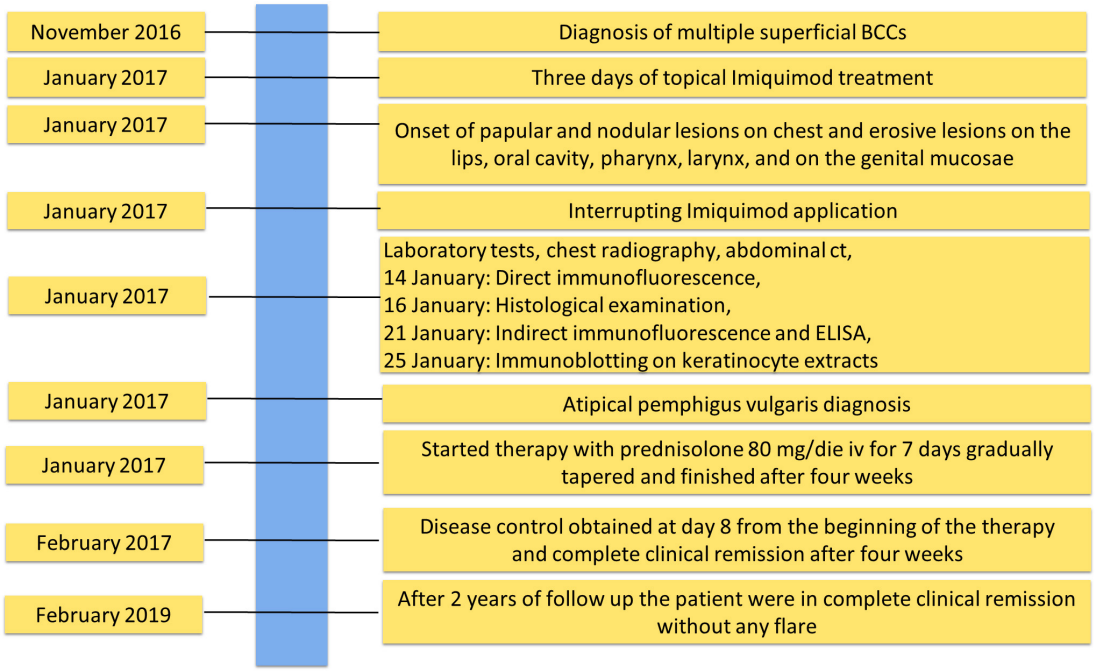

FIGURE 2
Timeline with relevant data about onset, diagnosis, and therapy of atypical pemphigus vulgaris.

detected as native protein by immunoprecipitation assay (11). Thus, the 170 kDa antigen remains an unknown atypical pemphigus autoantigen and further studies are needed to characterize it.

Hypothetically, Imiquimod might induce pemphigus involving overproduction of IFN-alfa by dendritic cells and keratinocytes stimulated by TLR-7 with consequent induction and maintenance of autoreactive B-cells. However, it is worth mentioning that the increased levels of TNF-alfa, IL-1, IL-6, IL-10, and IL-12 have been detected in the serum of patients with pemphigus and increased serum levels of TNF-alfa, IL-1 and IL6 have been correlated with disease activity. In addition, anti–TNF-alfa was reported to be effective in the treatment of PV (12). Nevertheless, the development of PV 3 days following TLR7 stimulation suggests that the Imiquimod treatment unmasked subclinical disease. In fact, people who undergo Imiquimod therapy hardly ever develop pemphigus, suggesting that specific predisposing factors are needed. It could be hypothesized that the pre-existence of low titers of circulating autoantibodies in predisposed individuals, for example with specific human leukocyte antigen haplotype, together with the cytokine milieu induced by the Imiquimod therapy may favor pemphigus development.

A limitation of our study was the inability to characterize the 170 kDa antigen identified by IB on keratinocyte extracts. However, the strength of our study is the thorough immunological characterization of the patient, which is lacking in almost all the studies in literature.

Conclusion

In some patients, topical application of imiquimod could induce pemphigus. Future studies could be carried out to assess the plausibility of the hypothesis that in the presence of multiple and/or voluminous BCC, sequential treatment with Imiquimod could reduce the risk of high absorption and adverse events.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FrM and GD contributed to the conception and design of the study. DC, LF, and SP collected the clinical data and information. DC wrote the first draft of the manuscript. FeM, AS, and SR performed laboratory analysis, ELISA, and histology. FrM, GD, SR, and DC wrote sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Funding

This study was supported by the "Progetto Ricerca Corrente" and "Ricerca Finalizzata" (No. 12367807) of the Italian Ministry of Health, Rome, Italy.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 02 December 2022
DOI 10.3389/fmed.2022.1048480

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 19 September 2022
ACCEPTED 21 November 2022
PUBLISHED 02 December 2022

CITATION
Buttgereit T, Fijen LM, Vera C, Bergmann K-C, Maurer M and Magerl M (2022) Case report: Recurrent angioedema: Diagnosing the rare and the frequent. *Front. Med.* 9:1048480. doi: 10.3389/fmed.2022.1048480

Case report: Recurrent angioedema: Diagnosing the rare and the frequent

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Hereditary angiodema with normal C1 inhibitor and unknown mutation (HAE-nC1INH-UNK), an exceedingly rare subtype of HAE, appears to be often diagnosed in patients who do not have this condition, but have mast cell-mediated angioedema. Here, we report two patients diagnosed with HAE-nC1INH-UNK by their physicians, who referred them to our center for treatment continuation with costly kallikrein-kinin-system targeted therapies. We describe how we established the correct diagnosis of recurrent mast cell-mediated angioedema after thorough investigation of both patients and initiated effective treatment with omalizumab. Also, we present and discuss the consensus criteria for diagnosing the very rare condition HAE-nC1INH in light of recent research and based on our own clinical experience. In conclusion, HAE-nC1INH-UNK should only be considered after more common differential diagnoses, i.e., mast cell-mediated angioedema, have thoroughly been investigated and ruled out. This approach reduces both the patients' disease burden and healthcare costs and contributes to meaningful research.

KEYWORDS

angioedema, recurrent, mast cell, omalizumab, normal C1INH, HAE

Introduction

In 2000, two research groups independently described families with hereditary angioedema (HAE) in which C1 inhibitor (C1INH) levels were unremarkable (1, 2). Subsequently, this disease was named HAE with normal C1 inhibitor (HAE-nC1INH, formerly also called HAE type 3). Initially, very little was known about the pathomechanism of HAE-nC1INH, but the lack of response to antihistamines, cortisone and epinephrine argued against a mast cell-mediated mechanism. In 2006, the mystery

seemed to be solved when a mutation in exon 9 of the *F12* gene was identified as the cause of HAE-nC1INH (3). Further research established that the development of angioedema (**Figure 1**) in these cases is due to uncontrolled formation of bradykinin. However, it soon became apparent that only a relatively small proportion of patients with HAE-nC1INH carried this disease-causing mutation, and the term HAE with normal C1 inhibitor of unknown cause (HAE-nC1INH-UNK) became common for patients with this phenotype but lacking a causative mutation. Although other causative mutations [*PLG* (plasminogen) (4), *ANGPT1* (angiopoietin 1) (5), *KNG1* (kininogen 1) (6), *MYOF* (myoferlin) (7), and *HS3ST6* (heparan sulfate 3-O-sulfotransferase 6) (8)] were identified in the past years, a molecular genetic confirmation of the very rare diagnosis of HAE-nC1INH still remains the exception.

In our experience from an Angioedema Center of Excellence and Reference (ACARE) (9), almost all patients with HAE-nC1INH are referred with the diagnosis of HAE-nC1INH-UNK based on their medical history, clinical symptoms, *ex juvantibus*, and the absence of laboratory findings indicative of other diseases. Since important and much more frequent differential diagnoses such as mast cell-mediated or ACE inhibitor-induced angioedema (AE-ACEI) cannot yet be diagnosed with the help of routine laboratory markers, but by using medical history, clinical symptoms, and therapeutic response, the diagnosis of HAE-nC1INH-UNK requires a cautious interpretation of the data and clinical experience. All too often, the supposedly well-defined diagnosis of HAE-nC1INH-UNK is chosen possibly to avoid, in the clinician's opinion, less well-defined diagnoses such as mast cell-mediated angioedema or even the so-called diagnosis of idiopathic non-histaminergic angioedema. As a result, patients with a presumed or already established diagnosis of HAE-nC1INH-UNK are increasingly referred to our center for further diagnostic workup and treatment initiation, with high expectations in patients and referring physicians.

In this paper, we report two patients diagnosed with HAE-nC1INH-UNK by their physicians, who referred them for treatment continuation with kallikrein-kinin-system targeted therapies. Here, we describe how we established the correct diagnosis and initiated effective treatment. Also, we present the criteria for diagnosing the very rare condition HAE-nC1INH in light of recent research and based on our own experience.

Case description

Case 1

A male patient born in 1966 moved from the United States to Berlin, Germany in January 2015 and presented to our clinic for the first time in March of the same year. In the letter from his previously treating physicians, the patient was diagnosed with HAE-nC1INH and we were asked to continue treatment with plasma-derived C1INH concentrate 1,000 units intravenously twice a week and icatibant, ecallantide, or epinephrine injector as needed in emergent cases. In the medical history taken at our ACARE, the patient reported recurrent angioedema since about the age of 20 years. Swellings had initially occurred on the tongue and face, and later the patient reported about swellings on the chest and painful abdominal symptoms, too. When asked in more detail, he had also experienced wheals from time to time. Since prophylactic treatment with 2nd generation H1-antihistamines up to the four-fold dose and corticosteroids had been insufficiently effective (at times the patient had to visit the emergency department several times a month), the diagnosis was changed from "recurrent idiopathic angioedema" to HAE-nC1INH some years before he was transferred. Mutational analysis was not performed, family history was negative, except a paternal uncle reported a once in his lifetime swelling. After the establishment of the diagnosis HAE-nC1INH, the patient received danazol at a dose of 200 mg; and when C1INH concentrate became available in the United States, the patient was switched to long-term prophylaxis with plasma-derived C1INH concentrate as described above. Other diagnoses according to physician reports included attention deficit hyperactivity disorder, gastroesophageal reflux, bipolar disorder, status post pulmonary embolism in March 2008, asthma, and vocal cord dysfunction. For treatment of these disorders, the patient was taking amphetamine dextroamphetamine, cholecalciferol, ciclesonide, fish oil, fluticasone, levocetirizine, methocarbamol, vitamin tablets, omeprazole, trazodone, and valaciclovir.

As the patient reported that since moving to Germany the swelling attacks had decreased significantly, he used treatment in the last months only as needed. Laboratory parameters obtained at his initial presentation confirmed normal C1INH activity and concentration (128%; 0.26 g/L), normal tryptase, and moderately elevated total IgE (5.79 μg/L; 139 KU/L). Although the patient was able to self-administer C1INH or icatibant, he occasionally came to the clinic for treatment and monitoring. On two of these occasions, our ACARE physicians observed anxiety and agitation, with shortness of breath and a marked expiratory stridor. After injection of icatibant, improvement occurred after about 30 min, just as after injection of C1INH concentrate. The patient asserted that these were the exact symptoms of his HAE disease. After each treatment, the patient could be discharged about 1 h after treatment. At the next regular appointment, we diagnosed the patient with both non-allergic bronchial asthma and mast cell-mediated angioedema in the setting of chronic spontaneous urticaria (CSU) refractory to antihistamines. Subsequently, we initiated treatment with omalizumab 300 mg subcutaneously every 4 weeks in June 2015. Regarding his non-allergic bronchial asthma, the patient received budesonide, formoterol (both once daily) and salbutamol (as required). Angioedema occurrence seized immediately, asthmatic symptoms markedly improved

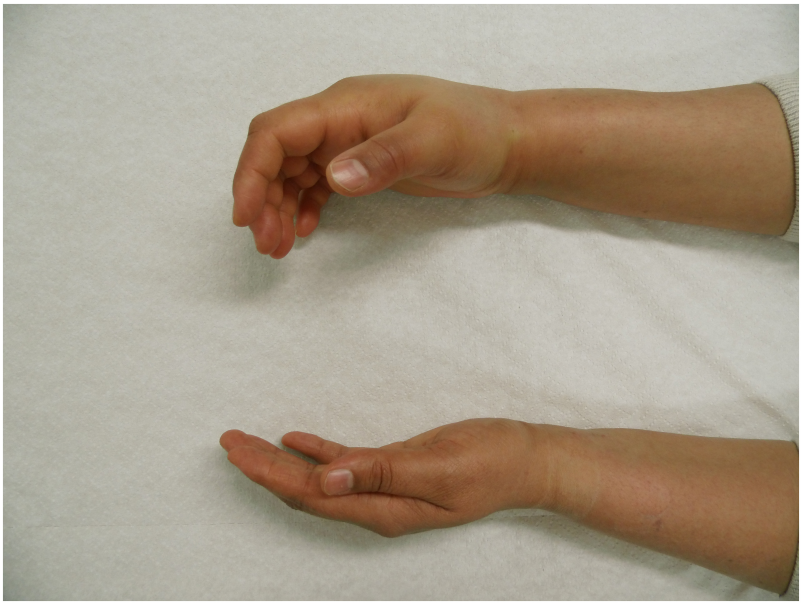

FIGURE 1
Angioedema of the right hand in a patient with hereditary angioedema due to C1 inhibitor (C1INH) deficiency (HAE-C1INH). Patient consent was obtained.

after a few weeks and almost completely disappeared in the further course. C1INH concentrate and icatibant no longer had to be used. Since the start of omalizumab treatment, the patient had no more angioedema attacks, except for once, when he attempted to prolong the injection interval of omalizumab. In August 2022, his disease control was complete as assessed by use of the angioedema control test (AECT, 16 points). Nevertheless, the impairment of quality of life was still considerable as assessed by use of the angioedema quality of life questionnaire (AE-QoL 53 points: Functioning: 0 Points, Fatigue/Mood: 65 Points, Fears/Shame: 91 Points, Nutrition: 12 Points), possibly overlaid by feelings of fear and impairment from his history of recurrent angioedema and/or comorbid bipolar disorder.

Case 2

A male patient born in 1958 moved to Berlin in September 2021 from another European country for almost 1 year for professional reasons. His referring physician, who had diagnosed HAE-nC1INH, reached out to us and asked us to continue treatment with lanadelumab 300 mg every 14 days, which had improved the patient's condition. The medical history taken at our ACARE confirmed that the patient had recurrent angioedema, which had started at the age of 56 years, with swellings have mainly occurring on the face, tongue, and genitals. Furthermore, the patient stated that swellings usually developed in the early morning hours, usually initially hemifacial. Prophylactical treatment with double-dose 2nd generation H1-antihistamines (cetirizine, bilastine) did not control the disease; and corticosteroids were never used. After the patient swelling attacks responded to icatibant several times and the attack rate increased significantly in the further course, he was diagnosed with HAE-nC1INH, and long-term prophylaxis with lanadelumab, 300 mg subcutaneously every 2 weeks, was initiated. With this, the patient observed clear improvement, and on-demand therapy with icatibant was no longer necessary. However, the patient was not completely symptom-free. When there was an unintended interval extension of lanadelumab for several weeks shortly after his relocation to Germany due to unresolved insurance issues, the symptoms worsened and regressed relatively slowly after re-initiation of lanadelumab. At his visit at our ACARE in February 2022, the patient scored four points (meaning uncontrolled disease) in AECT and 37 points in the AE-QoL. The patient's history also revealed that he had experienced wheals from time to time. In his family history, only his maternal grandmother had a history of infrequent ocular swellings. Laboratory parameters obtained at our ACARE confirmed normal C1INH activity and concentration (126%; 0.3 g/L), normal tryptase and elevated total IgE (7.05 μg/L; 320 kU/L). Molecular genetic testing for the genes ADGRE2, ANGPT1, CPN1, F12, KNG1, NLRP3, PLCG2, PLG, SERPING1, SPINK5, TNFAIP3 was negative with respect to mutations known to cause HAE. As an incidental finding, a genetic variant in PLCG2, c.656 A > G p.(Asp219Gly) of unclear significance was identified, which is associated with familial autoinflammatory cold syndrome-3, for which, however, there was no history or clinical evidence in the

patient. Based on the patients' medical history, clinical features, and his insufficient response to lanadelumab, we suspected mast cell-mediated recurrent angioedema due to CSU and initiated treatment with omalizumab in the approved dose; lanadelumab was discontinued. Already after the first injection with omalizumab, the patient was completely symptom-free, and he scored 15 points (well-controlled disease) in the AECT in June 2022. In September 2022, his disease control was complete (AECT 16 points), and the impairment of quality of life was minimal (AE-QoL 3 points).

Discussion

These two patient cases demonstrate that, as often reported, not only patients with HAE are misdiagnosed, i.e., with mast cell-mediated angioedema, and have a diagnostic delay, but that misdiagnosis of HAE can also happen in the other direction. In particular, HAE-nC1INH-UNK, an exceedingly rare subtype of HAE, appears to be often diagnosed in patients who do not have this condition, but have mast cell-mediated angioedema. In both cases presented here, the diagnosis of HAE-nC1INH was made despite features pointing to mast cell-mediated angioedema and without genetic testing. This led to significant consequences for the patients and caused high costs for the healthcare system. The correct diagnosis of HAE-nC1INH is challenging and there are several things that need to be considered, which we will discuss in more detail here.

Hereditary angioedema due to C1INH deficiency (HAE-C1INH) is an orphan disease, with an estimated prevalence of 1:50.000 (10). The prevalence of HAE-nC1INH, and even more specifically of HAE-nC1INH-UNK, is much lower, making it extremely rare. Meanwhile, other diseases that present with recurrent angioedema, such as mast cell-mediated angioedema and drug-induced angioedema, are much more common. Thus, epidemiologically, HAE-nC1INH-UNK should not be presumed until more plausible explanations for recurrent angioedema are ruled out (**Figure 2**). In 2012, an international expert panel developed consensus criteria for the diagnosis of HAE-nC1INH (11). First, HAE-nC1INH requires a history of recurrent angioedema in the absence of concomitant hives/wheals or concomitant use of a medication known to cause angioedema. Second, HAE-nC1INH should only be diagnosed with documented normal or near normal C4 levels, C1INH levels, and C1INH function. Third, the following features need to be present: (1) demonstration of a *F12* mutation that is associated with the disease, or (2) a positive family history of angioedema, and (3) documented evidence of lack of efficacy of continued high-dose antihistamine therapy (cetirizine at 40 mg/day or equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema). We consider the absence of concomitant

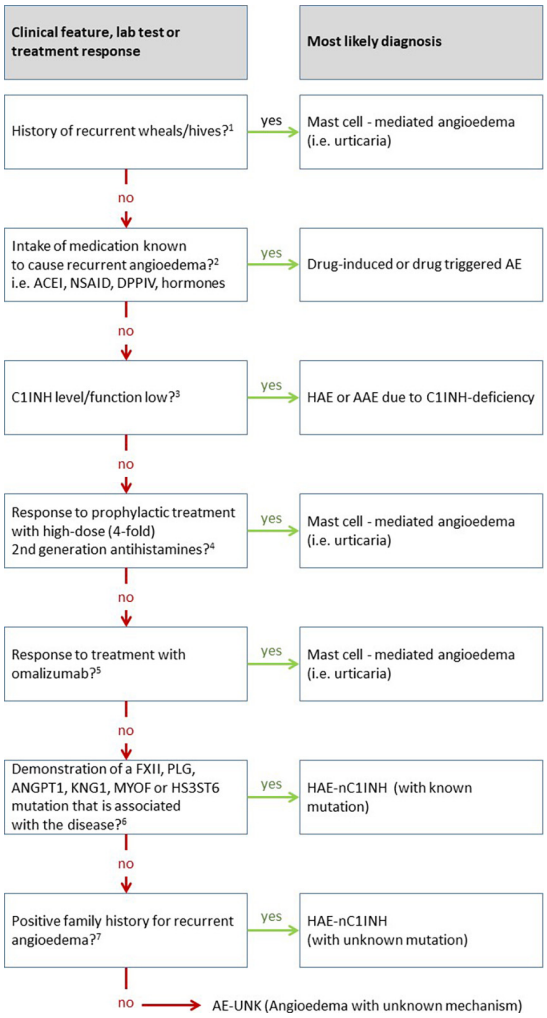

FIGURE 2
Overview of the differential diagnosis of hereditary angioedema (HAE) with normal C1 inhibitor (HAE-nC1INH). This diagram is adapted from the work of Zuraw et al. (11), updated based on own experience, newly approved therapeutic options in the meantime, and additional mutations discovered since then. [1]The recurrent occurrence of short-lived pruritic wheals and angioedema (AE) in recent patient's history is most suggestive of the presence of mast cell-mediated angioedema, i.e., chronic urticaria. However, the presence of wheals does not completely exclude the presence of another disease other like HAE, since urticaria, a very common disease, may also occur in association with HAE (approximately 1% of cases). [2]Medications can cause various forms of angioedema or trigger underlying diseases causing angioedema. For example, ACE inhibitors (ACEI) can cause swelling in otherwise healthy individuals but can also very reliably trigger swelling in patients with C1INH inhibitor deficiency. On the other hand, non-steroidal anti-inflammatory drugs (NSAID) can trigger swelling in otherwise healthy people, but also in many cases trigger angioedema flare-ups in patients with urticaria. [3]Angioedema due to C1INH inhibitor (C1INH) deficiency typically results in markedly decreased values for C1INH concentration and/or function. Borderline depressed results are not likely to attribute angioedema to C1INH deficiency. [4]Verification of the efficacy of antihistamines can be meaningfully evaluated by the administration of prophylaxis alone. The response of an as-needed therapy can rarely
(Continued)

FIGURE 2 (Continued)
be measured validly in individual cases *in praxi*. The duration of prophylaxis must be adapted to the frequency of angioedema, too short administration for false negative results. The dose should and can be increased to four times the usual daily dose for modern non-sedating 2nd generation antihistamines, e.g., up to 20 mg levocetirizine or desloratadine; 40 mg cetirizine, loratadine, rupatadine, or ebastine; 80 mg bilastine. It is recommended to use a lower dose (single or double the usual daily dose) before the maximum dose is applied, as this may also be sufficient in some cases. Non-efficacy of antihistamines does not justify the term non-histaminergic angioedema, since it is known that antihistamines are not sufficiently effective in more than 50% of cases of chronic spontaneous urticaria (CSU). [5]A significantly higher responder rate compared to antihistamines is seen with the use of omalizumab, both for wheals and angioedema. The response of omalizumab to angioedema is so reliable that in the absence of efficacy of omalizumab, the involvement of mast cells in the disease may be doubted. The use of omalizumab is a key step in the diagnosis of hereditary angioedema with normal C1 inhibitor when no underlying mutation for HAE-nC1INH is found. [6]Molecular genetic workup should ideally include all known mutations, or at least the commonly described ones involving factor 12 (FXII), plasminogen (PLG), or kininogen (KNG). In all likelihood, the number of causative mutations to be tested will continue to increase over the next several years. [7]If no causative mutation can be found in the molecular genetic analysis, the family history becomes of crucial importance. In this case, the family history must be clear and verifiable with regard to angioedema. For a definite diagnosis, several family members should be affected in more than one generation. The assumption that a single patient without family history suffers from angioedema as a result of a *de novo* mutation of an unknown gene is inadmissible.

wheals/hives as particularly relevant for diagnosing HAE-nC1INH. It is important to note that "concomitant," in this case, means the occurrence of wheals (hives) at any time during the course of the disease, but not necessarily at the same time as the angioedema is present. Wheals, in CSU patients who experience wheals and angioedema, oftentimes present in the absence of angioedema and vice versa. Approximately 20% of the general population experiences a single occurrence of wheals in their lifetime (12), unrelated to mast cell- mediated angioedema. On the other hand, up to 10% of many patients with mast cell-mediated angioedema do never experience wheals (13). Therefore, additional criteria as stated by Zuraw et al. (11) must also be met before HAE-nC1INH is diagnosed.

When the first two criteria are met and mutations in the *FXII* (3), *PLG* (4), *ANGPT1* (5), *KNG1* (8), *MYOF* (7), and *HS3ST6* (8) genes associated with HAE are ruled out, a positive family history is needed for the diagnosis of HAE-nC1INH. Importantly, the family history must be truly positive, with at least one, but preferably several family members, and ideally multiple generations affected. Other family members affected need to have experienced signs and symptoms indicative of HAE and responses to medication that are compatible with HAE. To put it bluntly, rumors that the grandmother once had swollen legs do not suffice. In the absence of a crystal-clear family history and a causative HAE mutation, the patient should be considered to have non-hereditary angioedema rather than HAE-nC1INH. In addition to a true positive family history, HAE-nC1INH-UNK may only be diagnosed if treatment with high-dose 2nd generation antihistamines has been shown to be ineffective. Here, several things are important to consider. First, even in *bona fide* mast cell-mediated angioedema, high-dose antihistamines have been shown to be ineffective in most patients, whereas, the vast majority patients with antihistamine-refractory angioedema respond to omalizumab (14–16). In other words, non-response to high-dose antihistamines does not necessarily indicate a non-mast cell mediated cause of recurrent angioedema. Therefore, we propose using ineffective treatment with omalizumab for at least 6 months as a criterion for diagnosing HAE-nC1INH. Although non-response to omalizumab does not rule out mast cell-mediated angioedema either, it does make it very unlikely. Of note, the efficacy of on demand use of antihistaminergic drugs to differentiate between mast cell-mediated and bradykinin-mediated recurrent angioedema is of little value. Reasons for this include the lack of validated, objective parameters to measure the efficacy of acute treatment of angioedema (17, 18) and the often-unrealistic expectations of both patients and physicians regarding the efficacy of these acute treatments. On demand antihistamine medication primarily prevents further progression of the swelling rather than promoting its regression. Moreover, the response to on demand treatment with antihistamines is dependent on the localization and severity of angioedema, the time between the start of swelling symptoms and the administration of the medication, and the dosage and route administration of the medication used. Given the enormous heterogeneity of angioedema symptoms and on demand use of antihistamines, it is downright impossible to accurately measure the responsivity to antihistamine treatment used at a single time. In contrast, the efficacy of angioedema prophylaxis can readily be measured with validated instruments, i.e., by using patient reported outcome measures (PROM) for disease activity [e.g., Angioedema Activity Score, AAS (19)], impact [AE-QoL (20)] and control [AECT (21)]. Hence, it is much more appropriate to evaluate the efficacy of prophylactic antihistaminergic therapy as opposed to on demand antihistaminergic medication for the treatment of an angioedema attack when assessing efficacy of antihistamines. This is recommended to be done with a high-dose antihistamine treatment (cetirizine 40 mg/day or equivalent) for 1 month or the duration of an interval in which at least three angioedema attacks are expected to happen in individual patients, whichever lasts longer (11).

Interestingly, both patients with recurrent mast cell-mediated angioedema benefitted from medication that acts very specifically on the kinin-kallikrein system, namely icatibant, C1INH concentrate, and lanadelumab. Even though the expectations of patients and physicians when using such drugs are very high and a pronounced placebo effect can be assumed, the described effects appear to go far beyond

this. In recent years, there has been increasing evidence that there are numerous functional cross-links between mast cells and the kinin-kallikrein system that challenge the classification of angioedema as either exclusively bradykinin-mediated or exclusively mast cell-mediated (22). These links between the two systems may explain, at least in part, the partial response of both patients. Moreover, the bradykinin B2 receptor antagonist icatibant inhibited carrageenan-induced angioedema in rats, which involves mast cells and histamine (23, 24). More recently, a clinical trial demonstrated efficacy for C1INH administration in human asthma (25), which is also, in part, mediated by mast cells and histamine. These findings and the partial response of our patients suggest that treatments for bradykinin-mediated angioedema including HAE may have benefit in mast cell-mediated angioedema, but this has not yet been investigated in controlled studies.

Misdiagnosis of HAE-nC1INH-UNK can have negative consequences in many respects, and the experience of our two patients underlines this. The diagnostic delay caused by misdiagnosing HAE-nC1INH-UNK prolongs disease burden, as patients will not be free of angioedema attacks. Recurrent angioedema attacks have been shown to greatly impact the quality of many aspects of patients' lives, not only physically, but also because of their effects on mental health, reproductive choices, social relationships, productivity, and work performance (26–30). Furthermore, on demand and prophylactic treatments for HAE-nC1INH (25) are very costly. When these medications are prescribed but have limited or no efficacy in patients incorrectly diagnosed with HAE-C1INH-UNK, healthcare costs unnecessarily increase. Last, but not least, incorrect diagnosis also impacts meaningful research. When the diagnostic criteria for HAE-C1INH are not met, outcomes of research investigating these patients are unreliable and thus unimplementable.

In conclusion, HAE-nC1INH-UNK should only be considered after more common differential diagnoses, i.e., mast cell-mediated angioedema, have thoroughly been investigated and ruled out. When HAE-nC1INH-UNK is considered as the explanation for recurrent angioedema, the consensus criteria, updated for mutations and modern treatments discovered after the consensus meeting took place, should be observed to the letter.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent for the publication of this case report.

Author contributions

MMg, TB, and LF contributed to the conception and design of the study and wrote the first draft of the manuscript. K-CB assisted in the diagnosis and therapy of patients. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 02 December 2022
DOI 10.3389/fmed.2022.1055703

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 28 September 2022
ACCEPTED 11 November 2022
PUBLISHED 02 December 2022

CITATION
Scholl S, Schuster D, Technau-Hafsi K, Stete K, Rieg S, May AM, Bogdan C and Schauer F (2022) Case report: Cutaneous pseudolymphoma caused by a *Leishmania infantum* infection in a patient treated with anti-TNF antibody for plaque psoriasis. *Front. Med.* 9:1055703. doi: 10.3389/fmed.2022.1055703

Case report: Cutaneous pseudolymphoma caused by a *Leishmania infantum* infection in a patient treated with anti-TNF antibody for plaque psoriasis

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For psoriasis, which affects up to 2% of the population and adalimumab is approved from the age of 4 years. Here, we present a middle-aged Italian man with long-term history of plaque psoriasis and psoriasis arthropathica and adalimumab therapy. He developed ulcers or nodules within the psoriatic plaques, resembling cutaneous infection with *Leishmania infantum*. TNF and other cytokines such as IL-12 and IFN-γ are central in the early control of the infection. Discontinuation of the anti-TNF-treatment resolved the infection without specific therapy.

KEYWORDS

skin pseudolymphoma, cutaneous leishmaniasis, anti-TNF therapy, adalimumab, skin ulceration

Introduction

Tumor necrosis factor (TNF) inhibitors have been in use for a variety of diseases since more than 20 years. Adalimumab is a human recombinant monoclonal immunoglobulin G1 antibody, which binds to both soluble and tissue-bound TNF, followed by its inactivation and degradation (1, 2). As TNF not only acts as a proinflammatory cytokine during chronic inflammatory diseases, but also is critical for the control of various intracellular pathogens, TNF antagonists are capable of causing reactivation of certain viral, bacterial, protozoan, or fungal infections (3, 4). For

psoriasis, which affects up to 2% of the population, adalimumab is approved from the age of 4 years under certain conditions (5). Here, we present a middle-aged Italian man with long-term history of plaque psoriasis and psoriasis arthropathica and adalimumab therapy. Following stays in his home country, he developed ulcers or nodules within the psoriatic plaques, resembling cutaneous pseudolymphoma in histopathology. Parasitological diagnostics revealed a cutaneous infection with *Leishmania infantum*, which clinically resolved without specific therapy following discontinuation of the anti-TNF-treatment.

Case description

A 42-year-old Italian patient with a 20-year history of plaque psoriasis and psoriasis arthropathica presented to our hospital with numerous ulcerations or nodules within his psoriatic lesions that had appeared 6 months earlier. He had been treated with subcutaneous methotrexate (25 mg per week) for the past 9 years and adalimumab (40 mg every other week) for the past 7 years. Topical treatment included halometasone 0.05% plus triclosan 1% cream and calcipotriol plus betamethasone dipropionate foam in the weeks before hospitalization.

The obese patient (BMI 39 kg/m^2) showed multiple psoriatic lesions characterized by erythemato-squamous plaques disseminated over the integument (PASI 16.6). Moreover, the patient showed erosive and partly ulcerating plaques and nodules, some of them covered by distinct brown crusts, at the right forearm, right knee, left flank and the abdomen (**Figures 1A,B**). Physical examination showed no pathological findings. There was no lymphadenopathy.

The histopathology of an externally performed lesion biopsy reported dermal T-cell infiltrates without evidence repeated of malignancy. Two repeat biopsies and histologies from morphologically different lesions on the right forearm and right flank revealed an interface dermatitis with pseudolymphomatous infiltrates, thickening of the epidermis, follicular hyperparakeratosis, and perivascular, periadnexal, superficially accentuated lymphocytic infiltrates with a preponderance of T cells (**Figures 2A,B**). Tissue clonality analyses demonstrated polyclonal IgH and TCR gamma chain gene expression, thus excluding lymphoma. Direct immunofluorescence did not detect any IgG, IgM, IgA, or C3 depositions. Syphilis serology, carried out due to numerous plasma cells in the tissue, yielded negative results. Moreover, an HIV infection, borreliosis and tuberculosis were ruled out by negative antibody or PCR tests. A serum sample was negative for antibodies against (extractable) nuclear antigens. Complement factors were within normal ranges. In hematoxylin-eosin (**Figure 1C**), Giemsa (**Figure 1D**) and Feulgen stains, intracellular *Leishmania* amastigotes with kinetoplasts were seen, which were identified by culture, miniexon PCR and restriction fragment length polymorphism-analysis as *L. infantum*. The patient also had a positive anti-Leishmania serology (maximum titer detected by indirect immunofluorescence using viable *L. major* promastigotes was 1:1,600). Since the patient originated from and repeatedly visited southern Italy, it is likely that he acquired the infection during his temporary stays.

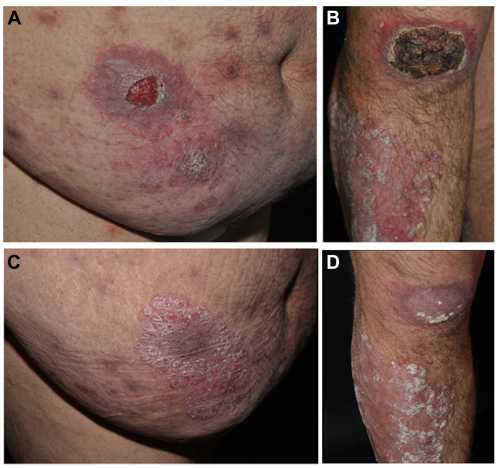

FIGURE 1
Panel **(A)** Ulceration (4 cm in diameter) within a psoriatic plaque on the right abdomen of the obese patient receiving anti-TNF therapy (adalimumab). Panel **(B)** Up to 10 cm pseudolymphomatous tumor surrounded by a psoriatic plaque on the right knee of the patient caused by cutaneous *Leishmania infantum* infection under anti-TNF therapy and erythematosquamous plaque on the right tibia. Panel **(C)** Erythematosquamous plaque on the right abdomen of the patient after cessation of adalimumab therapy. Panel **(D)** Erythematosquamous plaque on the right knee and shin of patients after cessation of adalimumab therapy.

The therapy with adalimumab was stopped, while treatment with methotrexate was continued (**Figure 2**). Interestingly, the ulcerations already started to heal under intensive topical treatment with salicylic acid, dithranol, and clobetasol propionate 0.05% ointment. Visceral involvement was excluded based on clinical parameters and sonography of liver and spleen. Therefore, we pursued a watch-and-wait strategy without specific therapy for leishmaniasis. The ulcerative skin lesions, which were clinically compatible with cutaneous leishmaniasis, completely regressed. After switching the systemic treatment to secukinumab (anti-IL-17A) or apremilast, the psoriatic lesions remained unaltered, but finally improved with ixekizumab (anti-IL-17A). During regular medical follow-up for almost 5 years the clinical condition of the patient remained stable (**Figure 3**).

Discussion

Cutaneous pseudolymphoma (CPSL) represents a heterogeneous group of benign lymphoproliferative reactions

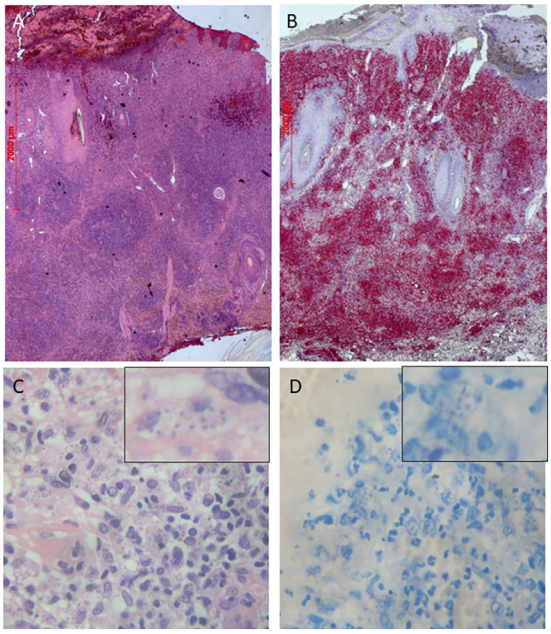

FIGURE 2
Panel **(A)** Histopathology shows a dense nodular, perivascular, periadnexal and interstitial infiltration of mainly T-cells and lymphocytes (Hematoxylin-eosin stain, ×25) Panel **(B)** Immunohistochemistry with CD3 antibodies (×25). Histopathology shows multiple intracellular amastigotes with peripheral nuclei and kinetoplasts in Hematoxylin-eosin stain Panel **(C)** and in Giemsa stain Panel **(D)** (×400 magnification each).

clinically and histologically mimicking lymphomas. Depending on the etiology, it can be subdivided into CPSL caused by infections (e.g., bacteria, viruses, parasites), drugs (e.g., anticonvulsants), foreign substances (e.g., vaccinations, tattoos), or other reasons (6). CPSL triggered by drugs (29%) and tattoos (26%) are the most frequent causes (6).

In our case, the patient's pseudolymphomas and ulcerations were due to an infection with *L. infantum* during immunosuppressive therapy for the treatment of psoriasis with adalimumab and methotrexate. *Leishmania* spp. are flagellated protozoan parasites that are transmitted by bites of sand fly vectors. Infections are endemic in almost 90 countries, including southern Europe and the entire Mediterranean coast (7, 8). Given the high number of positive leishmanin skin tests in Alicante, Spain (50% of adults, 10% of children), individuals may also be asymptomatic carriers of the parasite associated with transient or intermittent parasitemia (9, 10). There are several case reports describing pseudolymphoma and skin ulcerations as the cutaneous manifestation of leishmaniasis (11, 12) and infections are sometimes associated with anti-TNF therapy (3, 4). Cutaneous pseudolymphoma reactions can also be triggered by anti-TNF treatment in the absence of specific infections (8, 13–15). *Leishmania* spp. primarily infect and replicate within mononuclear phagocytes. Both the innate and adapted immune system are required for control. TNF and other cytokines such as IL-12 and IFN-γ are central in the early control of the infection. TNF and IFN-γ are responsible for the induction of leishmanicidal activity of macrophages, which is characterized by the production of reactive oxygen species, nitric oxide and metabolic changes of infected cells (16). The risk of *Leishmania* infections is therefore increased for individuals from endemic areas, who are treated with one or more immunosuppressive agents (e.g., glucocorticosteroids, methotrexate, azathioprine, or TNF inhibitors) (8, 17). *L. infantum* can cause cutaneous or visceral leishmaniasis, the latter being more frequent during childhood or in patients with poor immune status (e.g., HIV infection).

The anti-leishmanial treatment depends on the causative species, the clinical manifestation (cutaneous, mucocutaneous, or visceral manifestation) and the presence of underlying medical conditions (18). Bosch-Nicolau et al. (17) reported on 59 infected patients from the Mediterranean basin and found a more benign natural course in cutaneous leishmaniasis caused by *L. infantum* with spontaneous healing and local wound care after discontinuation of TNF inhibitors, especially if lesions were below 5 cm in diameter and in localized, non-disabling areas. On the other hand 14% of their treated

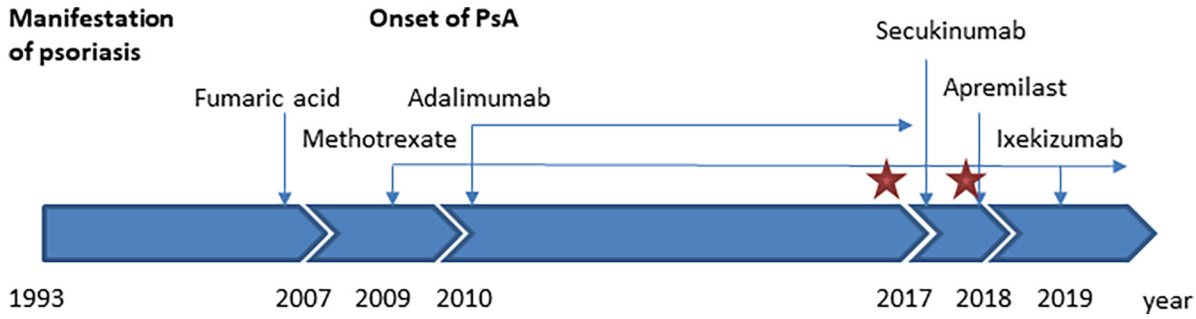

FIGURE 3
Time course of the patient's medical history, treatment, and *Leishmania infantum* infection. The red star marks the time of detection of *L. infantum* in skin biopsies. PsA, psoriasis arthropathica.

cases relapsed despite etiological therapy. Although our patient showed complex features of cutaneous infection without mucosal or visceral involvement, we only omitted TNF inhibitor therapy and implemented psoriasis specific topical treatment. The role of dithranol and its anti-proliferative and anti-inflammatory effects in cutaneous leishmaniasis remains unclear. The cytokines IL-17, IL-22, and IL-23 play an important role in the development of psoriasis and anti-IL-17A therapy significantly improved our patient's skin outcome (19). To date, no cases of leishmanial infection have been published in patients treated with anti-IL-17A antibodies (secukinumab, ixekizumab) or phosphodiesterase 4-inhibitors (apremilast).

Data even suggest for a protective effect of TH17 cells in controlling tissue parasitism (20).

Our case highlights the need for increased awareness for leishmaniasis in patients from endemic areas, who are treated with immunosuppressants such as TNF inhibitors. Serological screening can be considered to detect latent *Leishmania* infections, although it is of limited value in localized (muco-) cutaneous infections. Repeated skin biopsies should be performed if new atypical skin lesions arise. Histologically diagnosed pseudolymphomatoid reactions require further diagnostic tests to rule out causes such as leishmaniasis and other infections.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FS, DS, KS, and SR took care for the patient over the years. KT-H, AMM, and CB performed the diagnostics and were involved in making the diagnosis. SS drafted the manuscript. FS and CB edited the manuscript. All authors read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TYPE Case Report
PUBLISHED 02 December 2022
DOI 10.3389/fmed.2022.1047870

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Dermatology,
a section of the journal
Frontiers in Medicine

RECEIVED 19 September 2022
ACCEPTED 10 November 2022
PUBLISHED 02 December 2022

CITATION
Kita K, Kurokawa I, Hayashi D and
Hashimoto T (2022) Prurigo
pigmentosa clinically and
immunologically mimicking
autoimmune bullous disease: A case
report. *Front. Med.* 9:1047870.
doi: 10.3389/fmed.2022.1047870

Prurigo pigmentosa clinically and immunologically mimicking autoimmune bullous disease: A case report

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A 15-year-old Japanese male noticed brown macules on his back 9 months ago. Initial examination revealed reticulated infiltrative erythema and pigmentation with blisters on the erythema of the back. Histopathology showed blisters with eosinophil infiltration in the epidermis, and direct immunofluorescence showed negative results for immunoglobulin (Ig) G, Ig A, Ig M, and C3 in the epidermal basement membrane zone. Immunoserological tests revealed the presence of IgG antibodies against BP180, linear IgA disease antigen 1 (LAD-1), and laminin α3. The autoimmune bullous disease was suspected, and prednisolone at a concentration of 20 mg/day (0.3 mg/kg/day) was started. When the prednisolone dose was reduced to 10 mg/day, erythema and blisters recurred. The patient was diagnosed with prurigo pigmentosa based on clinical features and was treated successfully with oral doxycycline hydrochloride hydrate and topical tacrolimus ointment. This is the first case of prurigo pigmentosa with blisters in which autoantibodies to the epidermal basement membrane zone were found, which might be secondary non-pathogenic antibodies.

KEYWORDS

autoantibodies, autoimmune bullous diseases, immunoblotting, prurigo pigmentosa, bullous pemphigoid

Introduction

Prurigo pigmentosa, first reported in 1971 by Nagashima (1), generally presents with a highly pruritic urticarial and erythematous rash with recurrent prurigo-like erythematous papules on the back, chest, and neck that leave a coarse reticulated pigmentation (1, 2). It is more commonly observed in women aged 20–30 years, with a male-to-female ratio of 1:4–6.2. Even though the true etiology of the disease remains unknown, prurigo pigmentosa may be linked to diet-related hyperketonemia, eating disorders, and diabetes mellitus (3), as well as sweating and friction caused by clothing.

In this report, we present a case of prurigo pigmentosa with blisters that required differentiation from autoimmune bullous disease.

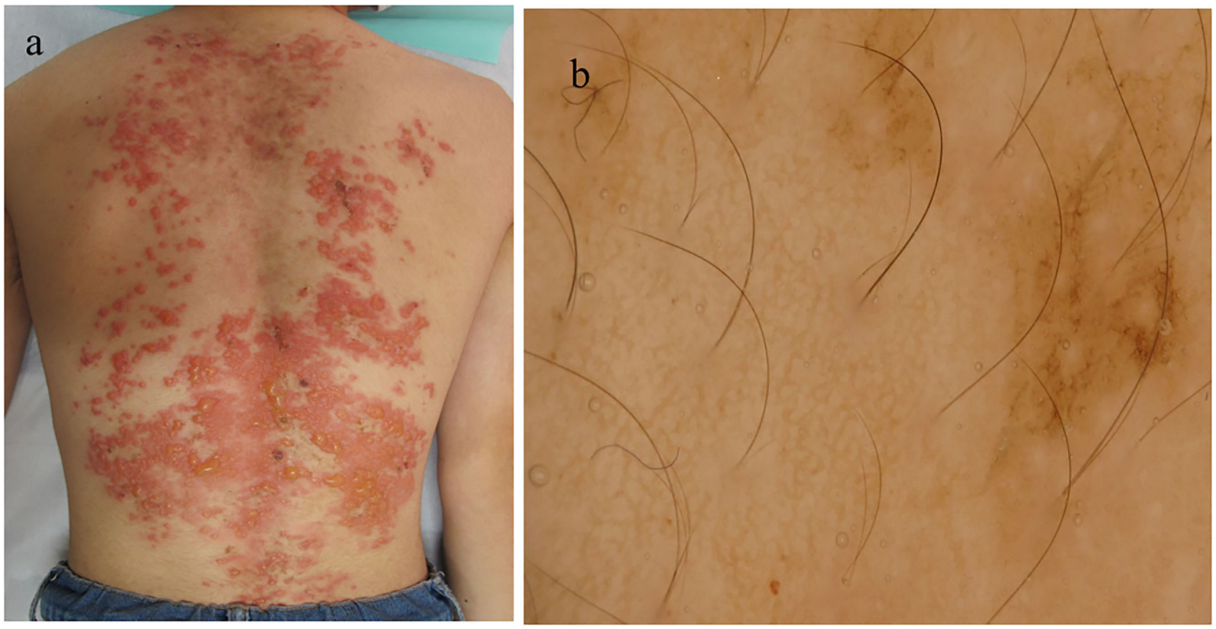

FIGURE 1
Clinical and histopathological features of the patient during the first visit. **(a)** Clinical features on the back. **(b)** Dermoscopic features.

Case report

A 15-year-old Japanese male first developed brownly pigmented macules on the trunk 9 months before his first visit. The skin lesions continued upon topical steroid therapy and then worsened with new blister formation despite treatment with minocycline hydrochloride (100 mg/day). During his first visit, a physical examination revealed extensive exudative erythema and slight pigmentation in a reticulated pattern on the back (Figure 1a). On the erythema, tense and flaccid blisters sized 5–20 mm were observed. His medical and family histories were unremarkable. A dermoscopy of the pigmented area showed a brownish-brown pigment network (Figure 1b). The Darier's sign was negative. The bacterial cultures of the blister content showed positive for *Staphylococcus aureus* (1+).

The results of blood counts and various biochemical tests were unremarkable. The results of anti-nuclear antibodies were negative, and the results of the urinary tests, including urinary ketone bodies, were normal. Histopathology of the biopsy taken from the blistering skin lesion revealed blister formation with eosinophil infiltration in the epidermis (Figures 2a,b). Toluidine blue staining and histochemistry for the c-kit yielded negative results. These histological results, in conjunction with a negative Darier's sign, excluded the diagnosis of mastocytosis and urticaria pigmentosa.

We also performed various diagnostic serological tests for autoimmune bullous diseases, which are routinely performed at our institute (4). Indirect IF of normal human skin sections was negative for both IgG and IgA antibodies (Figure 2c), whereas indirect IF of 1M NaCl-split normal human skin sections showed very weak IgG reactivity on both the epidermal and dermal sides of the split, but no IgA reactivity was detected (Figure 2d).

Enzyme-linked immunosorbent assay (ELISA; MBL, Nagoya, Japan) showed a weak positive reactivity to the BP180 NC16a domain (index 14.5, a cut-off value of <9.0), but was negative for BP230 ELISA (index 0, a cut-off value of <9.0) and type VII collagen (index 2.0, a cut-off value of <6.14). A chemiluminescence enzyme immunoassay (CLEIA; MBL, Nagoya, Japan) for BP180 (5.0 IU, normal 0–8.9) and desmogleins 1 and 3 were all negative.

Immunoblotting analyses showed that IgG, but not IgA, antibodies reacted with the recombinant protein (RP) of the BP180 NC16a domain (Figure 3a); IgG, but not IgA, antibodies reacted with the 120 kDa linear IgA disease antigen 1 (LAD-1) in the concentrated culture supernatant of HaCaT cells (Figure 3b); and IgG antibodies reacted with the 165 kDa laminin α3 subunit of laminin 332 RPs (Figure 3c). Immunoblotting analyses using normal human epidermal and dermal extracts and BP180 C-terminal domain RP showed no positive results for either IgG or IgA antibodies.

Upon the suspected diagnosis of autoimmune bullous disease, treatment with oral prednisolone (20 mg/day; 0.3

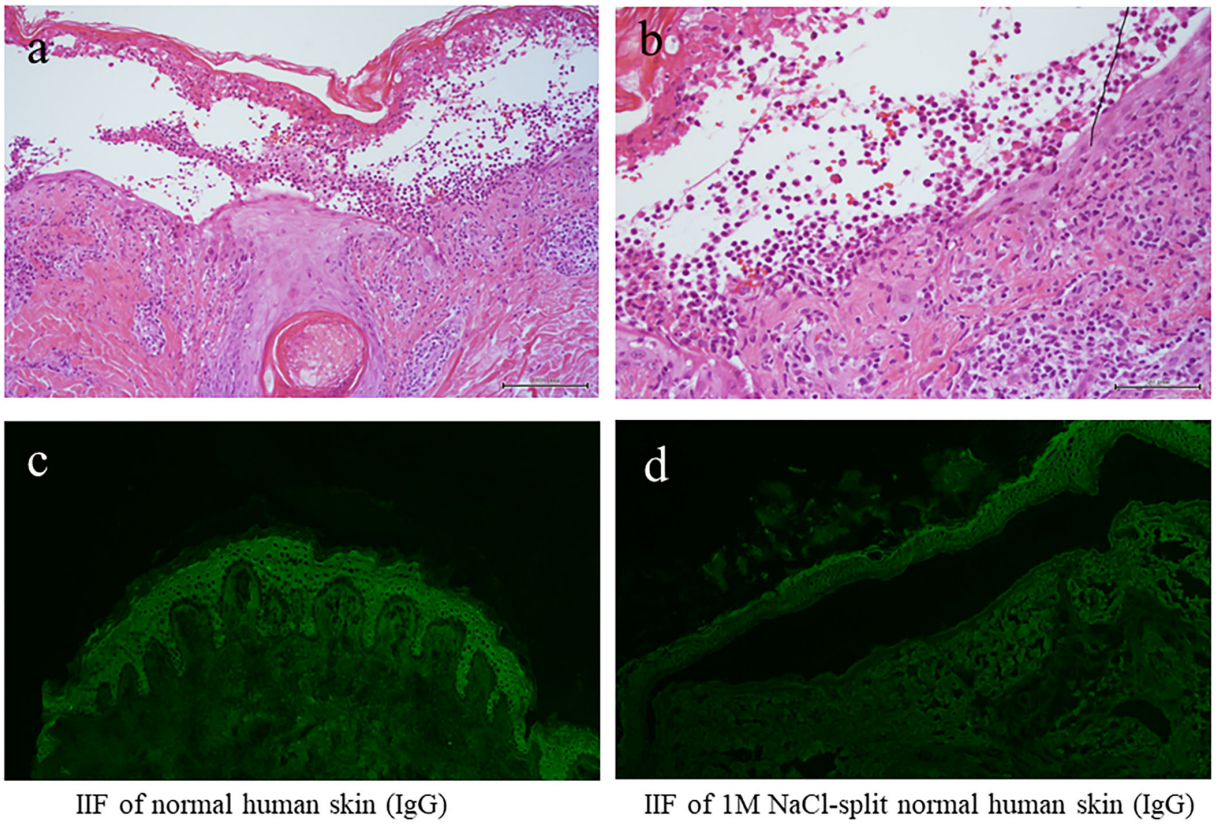

FIGURE 2
The results of histopathology and IF tests. **(a,b)** Histopathological features [H&E staining; magnifications: **(a)** x100; **(b)** x200]. **(c)** The results of indirect IF of a normal human skin section. **(d)** The results of indirect IF of 1M NaCl split skin section. IF, immunofluorescence.

mg/kg/day), fexofenadine hydrochloride (120 mg/day), and topical betamethasone butyrate propionate was started 9 days after the initial visit. Then, the skin lesions were almost cleared with post-inflammatory hyperpigmentation (PIH) with slight erythema (Figure 4a). When the prednisolone dose was reduced to 10 mg/day, multiple new erythema and blisters recurred on the back with PIH (Figure 4b). Based on the clinical features, a final diagnosis of prurigo pigmentosa was made, and treatment with doxycycline (100 mg/day), oral bepotastine besilate (20 mg/day), and topical tacrolimus ointment was initiated. While the prednisolone was tapered off, erythematous lesions disappeared, leaving reticulated pigmentation (Figure 4c). Thereafter, the patient showed no recurrence.

Discussion

Although prurigo pigmentosa usually shows no blisters, cases of prurigo pigmentosa with blistering skin lesions have rarely been reported (5–13). Kim et al. reported blister formation in two patients in their cohort of 50 patients with prurigo pigmentosa (5). Hoon et al. reported the case of a 13-year-old male patient with erythema and papules with blistering on the anterior chest and upper back, which were successfully treated with methylprednisolone succinate sodium ester (40 mg/day), doxycycline hydrochloride hydrate (200 mg/day), and tacrolimus ointment for 10 days (6). This case was negative for all anti-BP180 antibodies, antibodies against desmogleins 1 and 3, anti-nuclear antibodies, and anti-DNA antibodies. Yang et al. reported a 20-year-old female patient with pruritic erythematous and blistering skin lesions in a reticulated pattern on the back and neck that was successfully treated with minocycline hydrochloride without recurrence (7). Anti-skin antibodies were not detected. De Francesco et al. (8) and Wang and Xu (9) reported cases of bullous prurigo pigmentosa in which anti-skin antibodies were not detected. Wang and Xu (9), Matsumoto et al. (10), Requena Caballero et al. (11), Kubota et al. (12), and Sun et al. (13) also reported cases with numerous vesicles (12).

Thus, to the best of our knowledge, our patient is the first case of prurigo pigmentosa that developed extensive

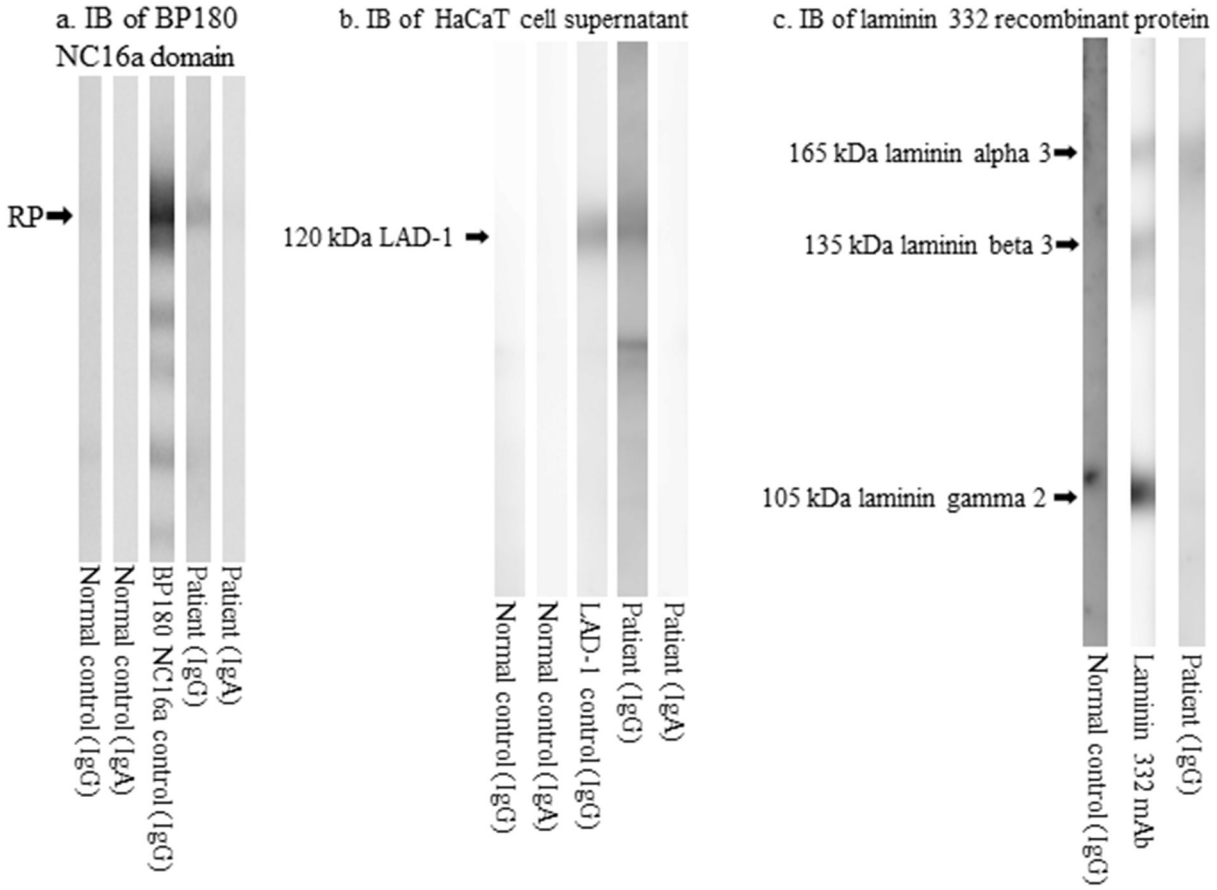

FIGURE 3
The results of immunoblotting analyses. **(a)** Immunoblotting of the RPs of BP180 NC16a domain showing IgG reactivity with the RPs. **(b)** Immunoblotting of concentrated culture supernatant of HaCaT cells showing IgG reactivity with the 120 kDa LAD-1. **(c)** Immunoblotting of RPs of laminin 332 showing IgG reactivity with the 165 kDa laminin α3. RP, recombinant protein; BP, bullous pemphigoid; LAD-1, linear IgA disease antigen 1; Ig, immunoglobulin.

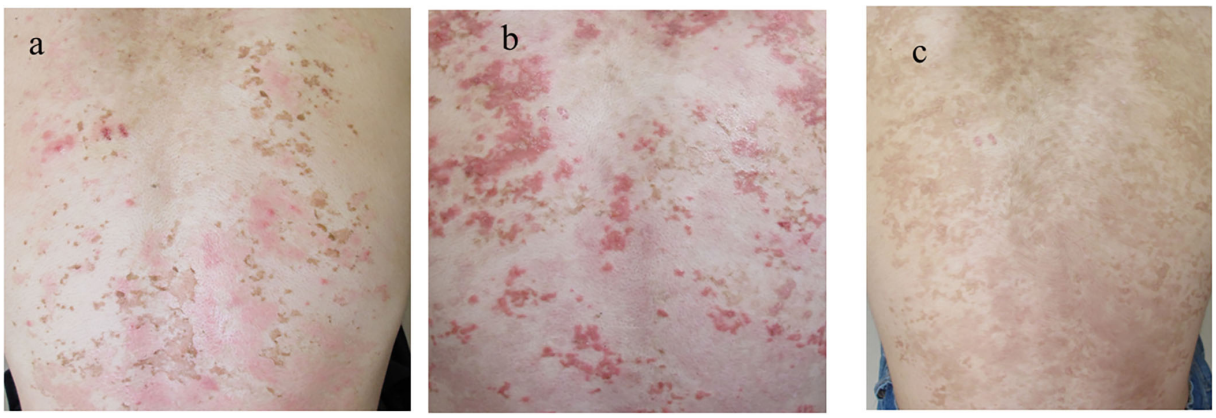

FIGURE 4
Clinical features during the disease course. **(a)** The skin lesions improved with the first treatment with PIH. **(b)** The recurrence of the skin lesions after the tapering of prednisolone. **(c)** The clearance of erythematous lesions with reticular pigmentation following the second treatment. PIH, post-inflammatory hyperpigmentation.

bullous lesions and showed autoantibodies against the cutaneous BMZ. However, Park et al. (14) reported three cases of non-bullous prurigo pigmentosa with anti-nuclear autoantibodies and suggested the autoimmune nature of prurigo pigmentosa.

Although diphenyl sulfone or dapsone is a therapeutic option for prurigo pigmentosa, minocycline hydrochloride and doxycycline hydrochloride hydrate, which have fewer side effects, have been used in recent years (2, 5, 6). Our patient had not shown improvement with minocycline hydrochloride and hoped to prevent minocycline-induced pigmentation. Therefore, we treated the patient with oral doxycycline hydrochloride hydrate and topical tacrolimus ointment with tapering of oral prednisolone, which quickly cleared the skin lesions, leaving reticulated pigmentation without recurrence. We speculated that the synergistic effects of oral doxycycline and topical tacrolimus would be superior to those of oral minocycline. So, doxycycline hydrochloride hydrate and topical tacrolimus should be good choices for treating prurigo pigmentosa with blister formation.

Since we suspected that our patient had autoimmune bullous diseases, we also performed various diagnostic tests for autoimmune bullous diseases (4), which revealed IgG anti-BMZ antibodies and IgG reactivity with the BP180 NC16a domain, LAD-1, and the laminin α3 subunits of laminin 332. The reason for positive IgG reactivity with recombinant protein of BP180 NC16a domain and LAD-1 but no reactivity in epidermal extracts may be that epitopes on BP180 molecule for IgG antibodies in this patient were exposed in the recombinant protein and LAD-1 but were hidden in the normal human epidermal extract.

Thus, our patient may have had a subepidermal autoimmune bullous disease. However, because the clinical features, particularly reticulated pigmentation, were characteristic of prurigo pigmentosa, the positive results of all the immunological tests were rather weak, and skin lesions in our case were cleared despite the tapering of oral prednisolone. We finally diagnosed our case with prurigo pigmentosa with blisters, and the anti-cutaneous BMZ antibodies were considered to be secondary non-pathogenic antibodies.

However, it is still possible that our patient had both prurigo pigmentosa and autoimmune bullous disease, and that the autoantibodies might be involved in blister formation. In this context, because doxycycline hydrochloride hydrate has recently been shown to be an effective therapeutic option for bullous pemphigoid (BP) (15), it is conceivable that doxycycline and topical tacrolimus also suppressed the autoantibody-causing BP-like blistering lesions in our patient.

Although the definite mechanism for autoantibody production in our patient is currently unclear, autoantibodies may have been produced by exposure to BMZ antigens after damage to the epidermis due to severe inflammation of prurigo pigmentosa. Antibodies against BP antigens were detected in elderly individuals without blistering skin diseases, probably because of the breakdown of immune tolerance due to aging (16). However, this notion cannot be applied because our patient was a 15-year-old.

Indirect IF detected circulating IgG antibodies reactive with the epidermal side of 1M NaCl split skin where BP180 was present. ELISA and immunoblotting showed IgG reactivity with the BP180 NC16a domain and LAD-1 (a truncated form of the C-terminal domain of BP180), confirming the presence of IgG anti-BP180 autoantibodies in our case, which might be involved in the pathogenesis of our case. In contrast, the significance of IgG antibodies to the 165 kDa laminin α3 subunit is obscure because indirect IF did not show IgG reactivity with the dermal side of 1M NaCl-split skin, where laminin 332 is present. Thus, anti-laminin α3 subunit antibodies may not be relevant in our case. Anti-BP180 NC16a antibodies were detected by ELISA but not by CLEIA. This phenomenon is occasionally observed, and we suggest that it is caused by the lower sensitivity of CLEIA than that of ELISA (17).

In conclusion, we presented the case of a boy with rare prurigo pigmentosa with blistering who showed IgG autoantibodies to the epidermal BMZ. Further case series for more cases on this condition are warranted to elucidate the pathogenic role of autoantibodies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

KK, IK, and TH wrote the original draft and treated the patients accordingly. DH and TH contributed to the immunological methods. All authors have reviewed the

manuscript. All authors have contributed to the manuscript and approved the submitted version.

Acknowledgments

The authors thank Mako Mine for her technical assistance.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 05 December 2022
DOI 10.3389/fmed.2022.1046820

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 17 September 2022
ACCEPTED 21 November 2022
PUBLISHED 05 December 2022

CITATION
Tozaki N, Tawada C, Niwa H, Mizutani Y, Shu E, Kawase A, Miwa Y, Ohnishi H, Sasai H, Miyako K, Hosokawa J, Kato A, Kobayashi K, Miyazaki T, Shirakami Y, Shimizu M and Iwata H (2022) A case of VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) with decreased oxidative stress levels after oral prednisone and tocilizumab treatment.
Front. Med. 9:1046820.
doi: 10.3389/fmed.2022.1046820

A case of VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) with decreased oxidative stress levels after oral prednisone and tocilizumab treatment

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VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome has recently been described as an autoinflammatory disease associated with severe adult-onset inflammatory manifestations. The various clinical manifestations include recurrent high-grade fever, neutrophilic dermatoses, cutaneous vasculitis, chondritis of the ear and nose, pulmonary infiltrates, cytopenia, uveitis, gastrointestinal pain or inflammation, aortitis, hepatosplenomegaly, and hematological disorders. VEXAS syndrome is caused by somatic mutations of the ubiquitin-like modifier activating enzyme 1 (*UBA1*) gene in myeloid-lineage cells. It is characterized by vacuolated myeloid and erythroid progenitor cells seen by bone marrow biopsy. We report the case of a 64-year-old Japanese man with VEXAS syndrome. At age 63, he was referred to us with a recurrent erythema on the hands associated with a general fever of 38–40°C that had persisted for 4 or 5 days and had recurred about once a month for a year. The skin rash appeared 2 or 3 days after the onset of each fever episode. Computed tomography (CT) of the chest revealed bilateral hilar lymphadenopathy (BHL), and the mediastinal lymph nodes were swollen. Sarcoidosis was suspected but was ruled out by several tests. Laboratory examinations showed elevated inflammatory markers. Bone marrow examination showed the vacuolization of myeloid precursor cells. A skin biopsy revealed dense dermal, predominantly

perivascular, infiltrates. These consisted of mature neutrophils admixed with myeloperoxidase-positive CD163-positive myeloid cells, lymphoid cells and eosinophils. Sequencing analysis identified the somatic UBA1 variant c.122T > C, which results in p.Met41Thr. Treatment with oral prednisone (15 mg/day) and monthly intravenous tocilizumab injections (400 mg) completely resolved the symptoms. Neutrophils are a major source of reactive oxygen species, and the present case demonstrated numerous neutrophilic infiltrates. We hypothesize that the patient might have had elevated derivatives of reactive oxygen metabolites (d-ROMs). d-ROM quantification is a simple method for detecting hydroperoxide levels, and clinical trials have proven it useful for evaluating oxidative stress. In this study, we measured serum d-ROM before and after oral prednisone and tocilizumab treatment. The levels decreased significantly during treatment.

KEYWORDS

VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory diseases, somatic, tocilizumab

Introduction

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is the first example of an autoinflammatory disease arising exclusively from somatic mutations and is one of an emerging class of acquired errors of immunity. Although this disorder was only first reported in 2020, hundreds of patients have been identified (1–5). VEXAS syndrome is caused by pathogenic variants in ubiquitin-like modifier activating enzyme 1 (*UBA1*), a gene on the X chromosome that encodes UBA1, and these mutations are restricted to myeloid-lineage cells (1). Patients with this syndrome are characterized by adult-onset recurrent fever, neutrophilic dermatoses, leukocytoclastic vasculitis, polyarteritis nodosa, ear and nose chondritis, venous thromboembolism, pulmonary infiltrates, gastrointestinal pain or inflammation, aortitis, hepatosplenomegaly, macrocytic anemia, elevated acute-phase reactants, myelodysplastic syndrome (MDS), multiple myeloma, and bone marrow vacuolization restricted to myeloid and erythroid precursor cells (1–5). The majority of the patients have myeloid lineage-restricted somatic mutations in *UBA1*, affecting the Met41 residue of the protein. These mutations promote the production of an inactive isoform (UBA1c) from a downstream translation site (Met67), resulting in hyperinflammation and decreased ubiquitylation (1, 5).

Autoinflammatory diseases are characterized by neutrophil activation. Neutrophils are a major source of reactive oxidative species (ROS) *via* NADPH oxidase. It is difficult to measure ROS directly due to their quick metabolization. However, derivatives of reactive oxygen metabolites (d-ROMs) are relatively easy to measure, and they reflect the hydroperoxide levels. We describe the clinical course of a VEXAS syndrome patient with a somatic *UBA1* variant who was treated with an oral steroid and anti-IL-6 therapy (tocilizumab) that lead to the resolution of the systemic symptoms. Interestingly, the elevated d-ROMs decreased significantly after these systemic therapies.

Case description

A 64-year-old Japanese man had a history of surgery for aspergilloma of the lungs at age 60. The patient works for a construction company. His father had died of pneumonia at age 59 and had been suspected of having leukemia. From age 62, he had had fevers of 38–40°C that had recurred about once a month, persisting for 4 or 5 days each time. At the previous hospital, sarcoidosis was suspected due to the swelling of the hilar and mediastinal lymph nodes and erythema nodosum-like cutaneous manifestations. He had been given 16 mg of methylprednisolone for 5 days at his previous hospital based on the diagnosis of erythema nodosum of the lower extremities. At age 63, he was referred to our dermatology department with the chief complaint of erythema on the hands. He was given colchicine for suspected autoinflammatory disease and immunodeficiency. After he started taking oral colchicine, the frequency of his fever decreased to once every 2 or 3 months. However, when the colchicine was stopped, the fever and skin rash flared up. Therefore, the colchicine was resumed and continued. The skin rash repeatedly appeared 2 or 3 days after the onset of

fever. At the age of 64 years and 10 months, the fever and skin rash flared up. Erythematous nodules and large and small plaques were seen on the upper extremities (Figure 1A), urticarial papules and plaques on the back (Figure 1B), and diffuse erythema on the abdomen (Figure 1C). A timeline of the clinical manifestations and treatments for more than 2 years is shown in Figure 2. Computed tomography (CT) of the chest revealed bilateral hilar lymphadenopathy (BHL), and the mediastinal lymph nodes were swollen. These were worse than at the previous hospital. Laboratory examinations showed elevated inflammatory markers. The C-reactive protein (CRP) level was elevated to 25.67 mg/dL (normal < 0.14 mg/dL), serum amyloid A protein (SAA) to 1480.0 μg/mL (normal < 8.0 mg/dL), and ferritin to 1034.0 ng/mL (reference range 39.9–465 ng/mL). Hemoglobin was 11.3 g/dL, hematocrit was 32.7%, total white blood cell count (WBC) was 4,840 cells/μL with a normal differential count, and the thrombocyte count was 95,000/μL. Serum protein electrophoresis (SPEP) was negative for M-protein. Rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, myeloperoxidase–anti-neutrophil cytoplasmic antibody (MPO-ANCA), and proteinase3-ANCA (PR3-ANCA) and cryoglobulins were negative. Thymus and activation-regulated chemokine (TARC) was elevated to 944 pg/mL (normal < 450 pg/mL), and IgE was elevated to 1315.0 IU/mL (normal < 232 IU/mL). A polymerase chain reaction (PCR) test was negative for COVID-19 during hospitalization, and the patient had no history of COVID-19 vaccination. Bone marrow examination showed the vacuolization of myeloid precursor cells (Figure 3A). We were able to confirm vacuolization in myeloblast, promyelocyte, myelocyte, and stab cell. A skin biopsy revealed perivascular inflammatory infiltrates in the entire dermis and in the subcutaneous fat (Figure 1D). The infiltrates consisted of mature neutrophils admixed with MPO-positive CD163-positive myeloid cells (Figures 3C,D), lymphoid cells, and eosinophils (Figure 1E). Sequencing analysis of whole peripheral blood identified the *UBA1* variant c.122T > C, which results in p.Met41Thr (Figure 3B). A detailed analysis of mutation mosaicism using the MiSeq Sequencing System (Illumina, Inc.) after the PCR amplification of *UBA1* showed that the variant was found in 49% of granulocytes, 21% of peripheral blood mononuclear cells (PBMCs), 46% of saliva, and 4% of urine (Figure 4). The differential included erythema nodosum, sarcoidosis, adult-onset Still's disease, and Sweet's disease. Although the patient met the diagnostic criteria for adult-onset Still's disease, we made the final diagnosis of VEXAS syndrome based on the clinical manifestations, laboratory tests, histological examinations, and genetic analyses. Treatment with oral prednisone (15 mg/day) was initiated and monthly intravenous injections of tocilizumab (400 mg) achieved the complete resolution of symptoms. At 3 months of follow-up, the patient was clinically stable with gradual improvements in his symptoms. He is currently taking 10 mg/day of prednisolone and we plan to taper the dose.

The d-ROM test measures the amount of hydroperoxide (R-OOH), which is a metabolite produced by active oxygen species and free radicals, in the sample *via* the colorimetric change of a chromogen. The d-ROM value is represented by the arbitrary unit "U.CARR." The oxidative stress that corresponds to each range of d-ROM values is as follows: normal, 200–300 U.CARR; borderline, 301-320 U.CARR; mild, 321–340 U.CARR; moderate, 341–400 U.CARR; high, 401–500 U.CARR; severe, ≥ 501 U.CARR. A commercial kit was used that involved the colorimetric determination of ROS (d-ROM) using the Free Radical Electron Evaluator (FREE; Health and Diagnostics, Naples, Italy). We measured serum d-ROM levels before and after the treatments in the preset patient. We used a commercial kit and 20 μl of patient serum, which was easy to measure. The d-ROM level was 500 U.CARR before treatment, and it decreased to 429 U.CARR with 4 days of 15 mg/day of oral prednisone. Four days after the intravenous injection of tocilizumab (400 mg), the level had decreased to 329 U.CARR. One month after intravenous tocilizumab, it had decreased to 168 U.CARR. The d-ROM level was significantly decreased after treatment with oral prednisone (15 mg/d) and the first intravenous injection of tocilizumab (400 mg) (Figure 3E). As shown in Figure 2, both CRP and neutrophil counts were elevated when VEXAS syndrome was active. The neutrophil count decreased from 4,429/μL before treatment to 2,808/μL 2 months after the start of treatment.

Discussion

Systemic corticosteroids and supportive care are the first-line treatment for the inflammatory symptoms and cytopenia of VEXAS syndrome. However, the identification of non-steroidal therapies is necessary for long-term management toward reducing the steroid dose and side effects. The steroid-sparing treatments that have been reported to have some success are methotrexate, mycophenolate, azathioprine, cyclophosphamide, and cyclosporine (2–4). Targeted agents, including anti-IL-1 (anakinra and canakinumab), anti-IL-6 (tocilizumab), anti-tumor necrosis factor α (TNF-α) (adalimumab, infliximab, and etanercept), and Janus kinase inhibitors, have been proposed as possible treatments for VEXAS syndrome (2–4). In fact, high serum levels of IL-6 have been observed in patients with VEXAS syndrome (1, 6). The effectiveness of tocilizumab for other inflammatory conditions with high levels of IL-6, such as adult-onset Still's disease, may suggest a role for this agent in the treatment of VEXAS syndrome as well (6). The present case also showed a systemic corticosteroid and an anti-IL-6 agent to have a significant and rapid effect. Kunishita et al. reported that the combination of tocilizumab and glucocorticoids allows the patients to continue treatment for at least 1 year without

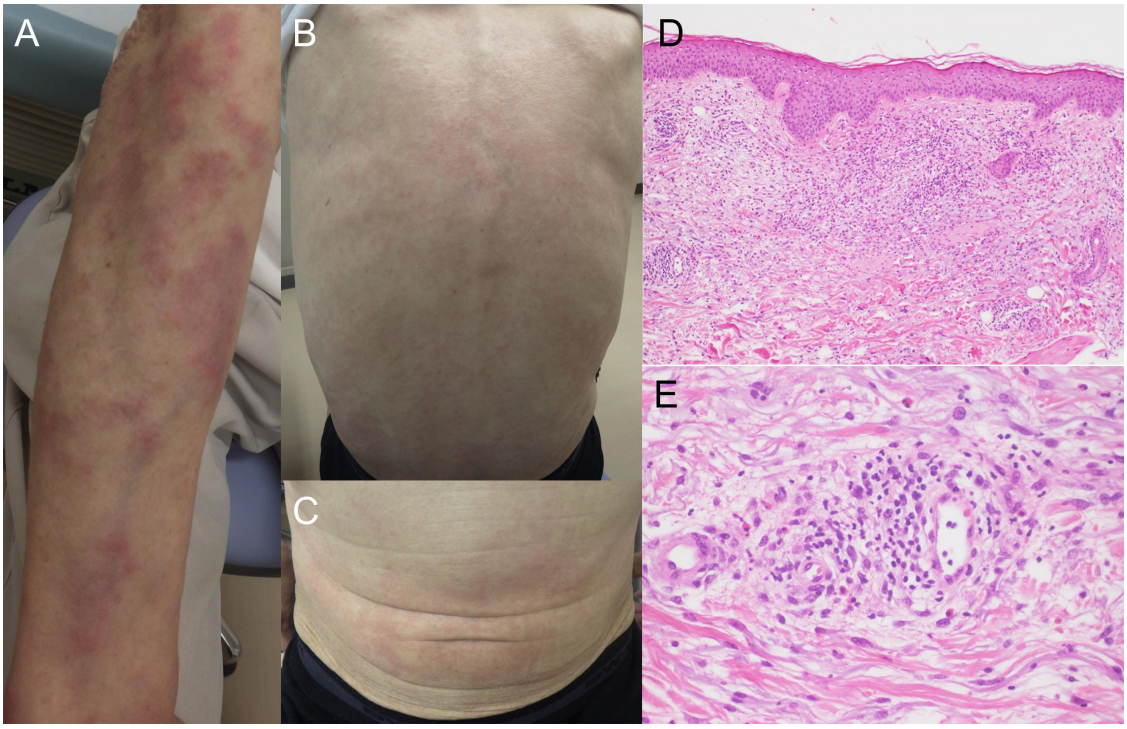


FIGURE 1
Clinical manifestations and histopathology. **(A)** Multiple erythematous plaques and nodular lesion on the upper limbs. **(B)** Urticarial lesions on the back. **(C)** Erythematous lesions on the abdomen. **(D)** Infiltration of inflammatory cells from the upper dermis to the subcutaneous fat (hematoxylin-eosin stain, original magnification × 100). **(E)** High magnification of dermal infiltrates around the perivascular region. The inflammatory infiltrates contain neutrophils, histiocytes, lymphoid cells, and eosinophils (hematoxylin-eosin stain, original magnification × 400).

significant disease progression. Glucocorticoids are able to be reduced from the start of tocilizumab (7). Bourbon et al. noted that most treatments were only transiently effective; the median time to the next treatment was 3.4 months for adalimumab, 3.9 months for corticosteroids, 7.4 months for methotrexate, and 8 months for tocilizumab (8). This patient may also relapse and should be followed up carefully. It is well known that significant side effects of tocilizumab may include the reactivation of tuberculosis; infection by opportunistic bacteria, fungi, and viruses; and intestinal perforation. Of note, there have been two reports of intestinal perforation in patients with VEXAS syndrome receiving tocilizumab (5, 6). Certainly, additional data and long-term follow-ups are needed to further validate these findings.

Obiorah et al. said, VEXAS syndrome patient's BM aspirate smears showed marked cytoplasmic vacuolization in hematopoietic precursors, including blasts and erythroid and myeloid precursors. Of note, vacuoles were predominantly found in early precursors (blasts, promyelocytes, and pronormoblasts). Vacuoles were also identified in eosinophils, monocytes, plasma cells, and megakaryocytes to a lesser degree. Lymphocytes were devoid of vacuoles (9). In this case we could confirm vacuolization in proerythroblast, promyelocyte, myelocyte, metamyelocyte. We could not confirm vacuolization in plasma cells which belong to the B cell lineage.

In previous reports of VEXAS syndrome, the *UBA1* variant was found only in neutrophilic dermatitis by skin biopsy, and not in leukocytoclastic vasculitis or septal panniculitis (10–14). This could lead to a distinction between clonal and paraclonal cutaneous involvements in VEXAS syndrome, which could in turn improve therapeutic outcomes (10). Zakine et al. reported that the infiltrates were perivascular and consisted of mature neutrophils with leukocytoclasia admixed with myeloperoxidase-positive CD163-positive myeloid cells with indented nuclei and lymphoid cells in eight patients with neutrophilic dermatosis (14). Sequencing analyses of bone marrow samples and skin lesion biopsies identified the same loss-of-function *UBA1* variant in all patients (14). VEXAS syndrome is caused by *UBA1* variants in myeloid lineage cells, including neutrophils and macrophages. CD68-positive M1 macrophages and CD163-positive M2 macrophages have been reported (14–16). M1-macrophages differentiate from inflammatory monocytes with TNF-α and interferon-γ, and are involved in controlling infections by pathogens and parasites. In contrast, M2 macrophages differentiate from tissue-resident monocytes with Th2 cytokines such as IL-4 and IL-13, and are involved in tissue repair. M2 macrophage polarization

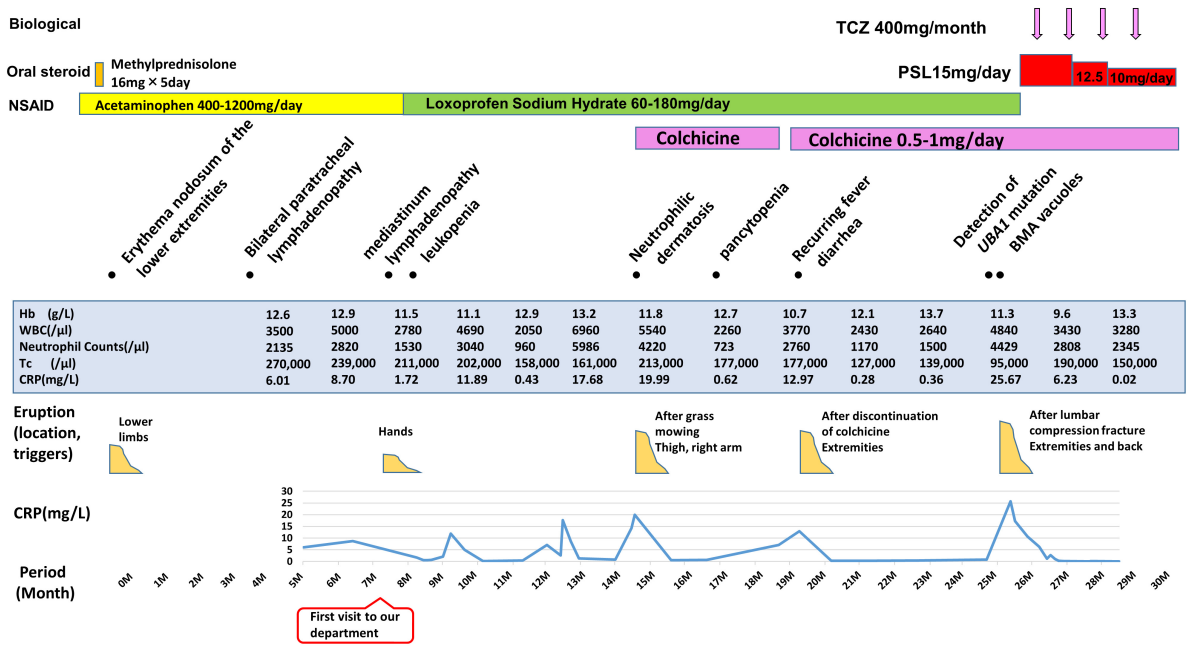


FIGURE 2
Overview of patient's disease course. TCZ, tocilizumab; PSL, prednisolone; NSAID, Non-Steroidal Anti-Inflammatory Drug; BMA, bone marrow aspirate; Hb, hemoglobin (normal range, 13.7–16.8 g/L); WBC, white blood cells (normal range, 3,300–8,600/μL); Tc, thrombocytes (normal range, 158,000–348,000/μL); CRP, C-reactive protein (normal < 3 mg/L).

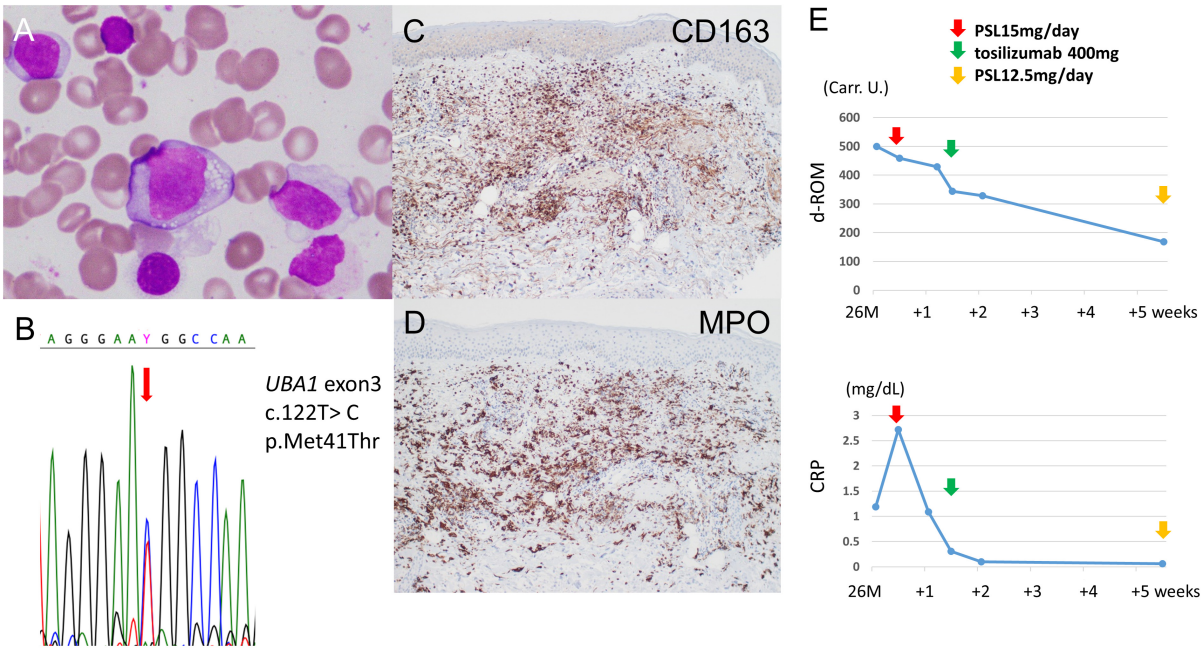


FIGURE 3
Additional tests for diagnosis and treatment. **(A)** Bone marrow aspirate smears show cytoplasmic vacuolization in myeloblasts (×40 magnification). **(B)** Sanger sequencing of genomic DNA derived from whole peripheral blood. The c.122T > C mutation is detected at position p.Met41 of the *UBA1* gene. **(C)** There are many CD163-positive cells, suggesting macrophages and histiocytes in the dermis (CD163 immunostaining, original magnification × 100). **(D)** The majority of infiltrates are MPO-positive (MPO immunostaining, original magnification × 100). **(E)** Serum d-ROM level before and after treatment. The d-ROM levels are expressed in Carratelli units (Carr. U.). The d-ROM levels decreased significantly after treatment with oral prednisone (15 mg/d) and the first intravenous injections of tocilizumab (400 mg).

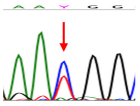
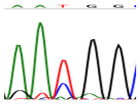
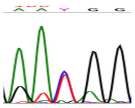
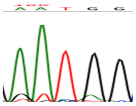
Sample	Sanger method	Total depth	Mutation mosaicism
Granulocyte		50657	49%
PBMC		58642	21%
Saliva		65685	46%
Urine		66089	4%
Control		68959	0%

FIGURE 4
Quantification of mosaicism. *UBA1* somatic variants of granulocytes from peripheral blood, peripheral blood mononuclear cells (PBMCs), saliva, and urine. Mutation mosaicism was analyzed by using the MiSeq Sequencing System (Illumina, Inc.) after polymerase chain reaction (PCR) amplification of the target. The target is the *UBA1* (NM_003334.4) missense mutation c.122T > C (p.Met41Thr) on chromosome X (47199052 T/C). Total depth and mutation mosaicism were measured by bam-readcount (ver 0.8.0). A commercial genome was used as a control.

is closely related to Th2 immunity (17). In this case, M2 macrophages might be mainly involved in the pathogenesis based on histological MPO-CD163-positive cell infiltrates and elevated serum levels of TARC and IgE. The patient had a history of surgery for pulmonary aspergillosis. He had no history of bronchial asthma, but it is possible that he was allergic and had elevated IgE, as in allergic bronchopulmonary aspergillosis.

Neutrophils generate ROS and are involved in various functions, including cell signaling homeostasis, and carcinogenesis. We evaluated the oxidative stress levels by measuring the d-ROMs. d-ROM quantification is a simple method for detecting hydroperoxide levels, and clinical trials have shown the d-ROM test to be useful for evaluating oxidative stress (18). d-ROM levels were decreased after treatment with oral prednisone (15 mg/d) and the first injections of tocilizumab (400 mg). ROS are commonly associated with neutrophil extracellular trap (NET) formation. It is possible that d-ROM levels were linked to changes in NET formation in the patient. Of course, it is difficult to conclude that d-ROM is an indicator of disease activity in VEXAS syndrome based on only this one case. The AutoInflammatory Disease Alliance (AIDA) keeps an international registry that includes VEXAS syndrome cases (19). We hope that further studies will be planned.

The diagnostic work-up for a patient with suspected VEXAS syndrome should include the characteristic cutaneous lesions (e.g., neutrophilic dermatitis, chondritis, vasculitis) and investigations of inflammatory markers (e.g., CRP, serum ferritin), a bone marrow biopsy, pulmonary imaging, pulmonary function tests, and the necessary investigations to rule out differential diagnoses. However, VEXAS syndrome can be confirmed only by the presence of a somatic *UBA1* variant, usually in peripheral blood. The dermatologist is often the first clinician to suspect a diagnosis of VEXAS syndrome. Early recognition and diagnosis may lead to a better prognosis and targeted treatments in the near future.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Author contributions

HI and HO involved with the conception of the work and participated in the revision of the manuscript. NT, CT, YS, AKaw, YMw, and HO contributed to the data acquisition. NT, CT, HI, HO, HS, KM, and JH contributed to the data analysis and interpretation. NT and CT drafted the manuscript. All authors approved the submitted version.

Funding

This study was supported by many of the staffers at Gifu University Hospital.

Acknowledgments

We would like to thank Kayoko Tanaka and Miyuki Kawai for preparing and testing the specimens. We are also grateful to Noriko Utsumi, Masaki Takazawa, and Osamu Ohara at the Kazusa DNA Research Institute for their technical assistance.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Case Report
PUBLISHED 08 December 2022
DOI 10.3389/fmed.2022.1072039

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 17 October 2022
ACCEPTED 23 November 2022
PUBLISHED 08 December 2022

CITATION
Xue G, Lili M, Yimiao F, Miao W, Xiaohong Y and Dongmei W (2022) Case report: Successful treatment of acute generalized pustular psoriasis of puerperium with secukinumab. *Front. Med.* 9:1072039. doi: 10.3389/fmed.2022.1072039

Case report: Successful treatment of acute generalized pustular psoriasis of puerperium with secukinumab

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Generalized pustular psoriasis (GPP) is a rare and severe form of psoriasis presenting with erythematous, aseptic pustules. Common systemic symptoms include fever and myalgias. The presentation of GPP resembles acute generalized exanthematous pustulosis (AGEP). However, the treatment of these two pathologies differs. While AGEP is self-limiting and treated with topical corticosteroids and constrain of systemic steroids. GPP treatment avoids corticosteroid, choosing acitretin, methotrexate, and cyclosporine as first-line agents. In this case report, a 27-year-old female with a medical history of AGEP presented to the hospital with extensive erythema and pustules. Complete blood count acute phase reactant analysis revealed an elevated white blood cell count and C-reactive protein (CRP). Two histopathological examinations revealed psoriatic hyperplasia of the epidermis with keratosis, along with Kogoj and Munro micro abscesses above the spina layer. Lymphocytic and neutrophilic infiltrate was present in the superficial derma layer along with vasodilation. The patient was diagnosed with GPP according to pathological and clinical criteria. Treatment was initiated with secukinumab because of the patient's failure to respond to systemic treatment with Acitretin, methotrexate, and cyclosporin. Following 2 weeks of therapy with 300 mg of secukinumab, the pustular lesions had resolved. This study indicates the potential efficacy of secukinumab as an effective therapy that can rapidly improve the clinical symptoms of GPP.

KEYWORDS

GPP, AGEP, secukinumab, interleukin-17A inhibition, biologic therapy

Introduction

On the first of December 2020, a 27-year-old female presented to our hospital with systemic erythema and pustular lesions for 2 months. Two months prior, the patient had a successful cesarean delivery at a local hospital and given penicillin and oxytocin post-operatively. The patient reported the gradual development of erythema spreading from her torso to her extremities. Afterward, dense millet pustules appeared in addition to desquamation of the skin. Examination of the electronic medical record indicated that the patient had been hospitalized with acute generalized exanthematous pustulosis(AGEP) in an outside hospital. However, treatment was refractory to antibiotics and corticosteroid. At admission, multiple yellow-white scales and crusts involved 80% of the body surface area (BSA). The dermatology life quality index (DLQI) at admission was 27 with a static global assessment of psoriasis (PGA) of 4.7. The patient reported erythema of the forearms and trunk with dense, large military pustules, with areas of desquamation (**Figure 1**). Routine laboratory testing revealed leukocytosis with neutrophilic predominance, elevated C-reactive protein (CRP) as well as elevations in hepatic enzymes. Two histopathological examinations revealed psoriatic hyperplasia of the epidermis with keratosis with Kogoj and Munro micro abscess above the spina layer. Lymphocytic and neutrophilic infiltrate was also present in the superficial dermis (**Figure 2**). Following histopathological and clinical criteria, the patient received a diagnosis of generalized pustular psoriasis (GPP).

On admission, the patient was treated with intravenous injection of levofloxacin and compound glycyrrhizin, oral acitretin and thalidomide for 3 days, but no improvement was observed. On the contrary, he showed worse signs including continuous enlargement of erythema and pustule areas, superficial red erosion of the buccal mucosa, and targeted lesions of edematous erythema on both lower limbs. In addition, he reported muscle pain throughout his body, decreased appetite, and depression as well. Following Japanese guidelines on the treatment of refractory GPP, the patient was given 300 mg of secukinumab after being informed of the risks of treatment. Within 72 h, the erythema, pain, scales, and pustules were significantly relieved, and the patient's mental state was improved (**Figure 3**). The DLQI decreased rapidly from 27 to 2 at week 3. After 5 injections once a week, maintenance therapy was initiated at a monthly basis for 3 months. A follow-up of 8 months showed no recurrence of skin lesions.

Discussion

This case report details a misdiagnosis of AGEP and the inappropriate use of corticosteroid treatment in an outside hospital. As such, the patient's condition worsened rapidly. Two epidermal biopsies showed psoriatic hyperplasia accompanied by incomplete keratosis, Kogoj microabscess, and dilatation and tortuosity of the superficial dermis. The histopathological features of AGEP include keratinocyte necrosis, dermal papillary edema, vasculitis, and perivascular eosinophil infiltration (1). GPP generally does not present with vasculitis and eosinophil infiltration. Therefore, the correct interpretation and clinical manifestations of early pathological diagnosis are of great significance for the treatment of GPP. This case reports the use of clinical judgment and histopathological analysis for the differential diagnosis between AGEP and GPP.

It has been reported that approximately 65% of GPP is secondary to psoriasis vulgaris (2). However, GPP also occurs in patients with no prior diagnosis of psoriasis, which can be induced by infection or in response to certain drugs. Specifically, prior studies have suggested that IV penicillin could induce GPP (3). The patient, who had no clear history of psoriasis, developed edematous erythema with pustular changes in his torso after intravenous penicillin infusion, which did not improve after discontinuation. Therefore, it is reasonable to conclude that GPP may have been induced by penicillin, which led to the early misdiagnosis of AGEP. This difference in treatment could have profound impacts for patients and should be assessed clinically prior to starting therapy.

First-line treatment for GPP currently includes acitretin, cyclosporine, methotrexate, or infliximab (4). In recent years, biologic agents targeting TNF-α, IL-1, IL-12/23p40, IL-17A, and IL-36 have been reported in the treatment of GPP (5, 6). Designed to target and neutralize IL-17A, secukinumab, a human monoclonal antibody, was evaluated for the treatment of GPP in a Phase III clinical study in Japan (7), and there are many real-world studies on pustular psoriasis in children (8, 9). Due to the patient's lack of response to standard therapy, the patient was given secukinumab for a total of 3 months. After the initial dose, disease progression was halted and recovery of the lesions began promptly, with a resolution of pustules and erythema in 72 h. An improvement of the dermatology-specific health-related quality of life was also observed.

Currently, there are no unified guidelines for the long-term use of Secukinumab for the treatment of GPP in China. This patient received a weekly dose of 300 mg subcutaneously on week's 0–4, followed by 300 mg every 4 weeks after (10). In this case, the lesions were completely cleared within 2 weeks of treatment with Secukinumab. The treatment duration was extended for a total of 3 months using the dosing schedule described above. At the 8 months follow up, no recurrence was

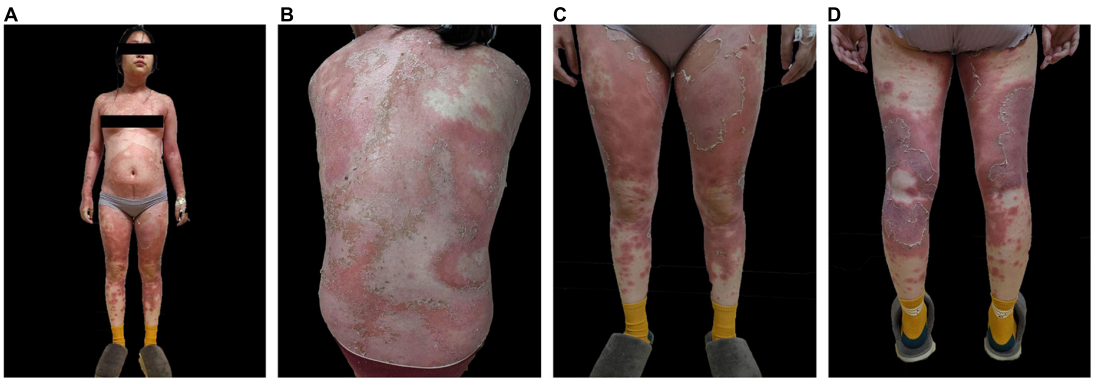

FIGURE 1
Pre-treatment skin images of **(A)** anterior skin lesions **(B)** posterior skin lesions **(C)** anterior lower extremities **(D)** posterior lower extremities.

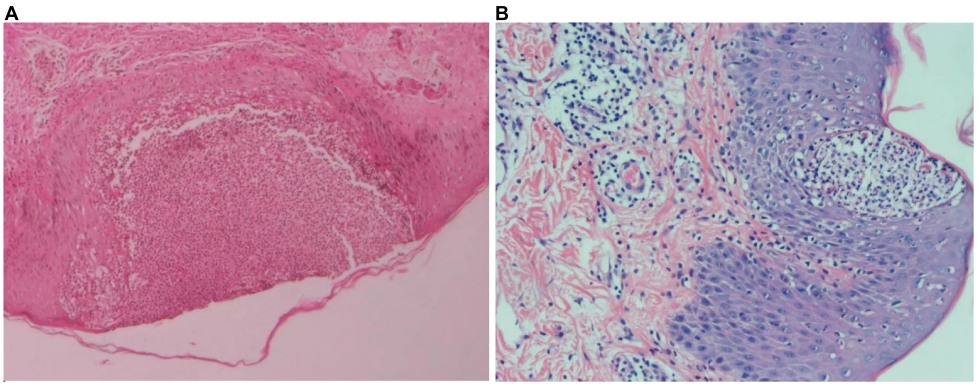

FIGURE 2
(A) Skin biopsy of the left lower limb with hematoxylin-eosin staining at 50× magnification. Squamous epithelial hyperplasia was observed with epidermal pustular formations. Kogoj abscesses can be seen at the pustular margin. The upper dermis showed lymphocytic infiltration and some dermal papillary edema. Perivascular infiltration and a small number of lymphocytes were also observed. **(B)** Skin biopsy of the left lumbar region with hematoxylin and eosin staining at 100× magnification. Squamous epithelial hyperplasia, Munro micro abscesses, and Kogoj abscesses were observed in the epidermis. A small amount of lymphocytic and neutrophilic infiltrate was observed in the upper dermis. Some dermal papillary edema, vascular dilation hyperemia and lymphocytic perivascular infiltration was also observed.

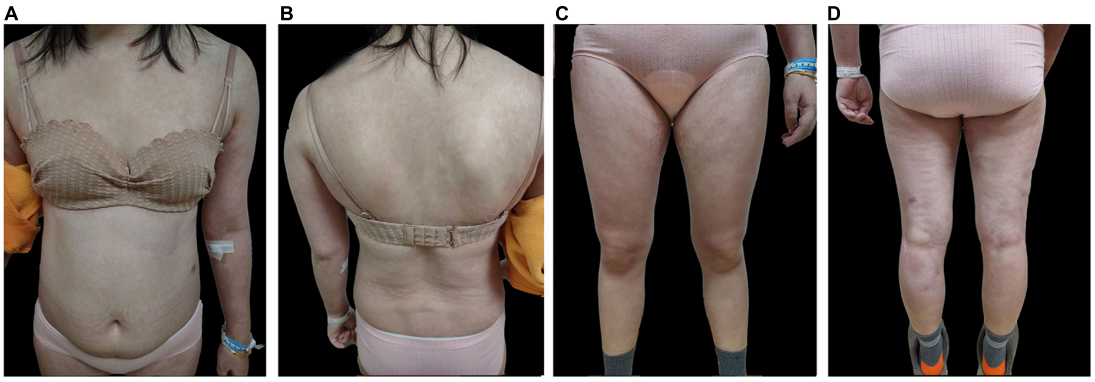

FIGURE 3
Post-treatment skin images of **(A)** anterior skin lesions **(B)** posterior skin lesions **(C)** anterior lower extremities **(D)** posterior lower extremities.

reported. As such, Secukinumab may serve as a viable therapy for severe refractory cases of GPP.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GX collected the data of the case and finished the manuscript. ML provided guidance of modifying the manuscript. FY and WM helped collect the data of the case. WD helped polish the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Zhejiang Key Laboratory of Dermatology of Integrated Traditional Chinese and Western Medicine [Project No. 2A11829 (Finance 201808)-01]. These funds made significant contributions to the study design, data interpretation, and writing of this manuscript.

Conflict of interest

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TYPE Case Report
PUBLISHED 08 December 2022
DOI 10.3389/fmed.2022.1086473

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 01 November 2022
ACCEPTED 21 November 2022
PUBLISHED 08 December 2022

CITATION
Costa BA, Zibara V, Singh V, Hamid O, Gandhi S, Moy AP and Betof Warner AS (2022) Case report: Later onset of NRAS-mutant metastatic melanoma in a patient with a partially-excised giant congenital melanocytic nevus. *Front. Med.* 9:1086473. doi: 10.3389/fmed.2022.1086473

Case report: Later onset of NRAS-mutant metastatic melanoma in a patient with a partially-excised giant congenital melanocytic nevus

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Despite recent advances in treatment and surveillance, metastatic melanoma still carries a poor prognosis. Large/giant congenital melanocytic nevi (CMNs) constitute a known risk factor for the condition, with the greatest risk for malignant transformation thought to be during childhood (median age at diagnosis of 3 years in a previous cohort). Herein, we present the case of a 30-year-old male who, after undergoing multiple excision/grafting procedures for a giant CMN as a child, was diagnosed with an *NRAS*-mutant, *MDM2*-amplified metastatic melanoma more than 20 years later. Response to ipilimumab/nivolumab immunotherapy, cisplatin/vinblastine/temozolomide chemotherapy, and nivolumab/relatlimab immunotherapy was poor. This case highlights the importance of lifetime monitoring with once-yearly dermatological examination (including lymph node palpation) in large/giant CMN patients, as well as the need for further clinical trials evaluating novel therapies for *NRAS*-mutant melanoma.

KEYWORDS

metastatic melanoma, congenital melanocytic nevi, giant nevus, *NRAS* mutation, MDM2 amplification

Introduction

According to GLOBOCAN 2020, cutaneous melanoma accounts for 1.7% of new cancer cases worldwide (1). In the US, melanoma is now the fifth most commonly diagnosed malignancy, with around 99,780 cases estimated for 2022 (2). Over the last decade, US mortality decreased by nearly 30%, in part due to Food and Drug Administration (FDA) approval of several targeted and immune-based agents for patients with advanced disease. Even so, overall survival (OS) for stage IV melanoma remains low (29.8% at 5 years), prompting continuous bench-to-bedside efforts to

develop novel therapies (3). Established risk factors for melanoma include a personal or family history of the malignancy, high socioeconomic status, Fitzpatrick skin phototype I-II, ultraviolet (UV) radiation by sun exposure or indoor tanning, and presence of acquired or congenital melanocytic nevi (CMNs) (4, 5).

With an estimated prevalence of 0.2–6% in worldwide literature, CMNs are benign proliferations of melanocytes often caused by postzygotic *NRAS* mutations *in utero* (6–9). Based on their projected adult size (PAS), these lesions can be classified as small (<1.5 cm), medium (1.5–20 cm), large (>20–40 cm), or giant (>40–60 cm) (9). CMNs >20 cm are uncommon, occurring in 1 out of every 20,000 births (8). The most frequent distribution pattern is bathing trunk (45.5%), followed by bolero (27.4%), back (13.6%), breast/belly (4.5%), body (4.5%), and body extremity (4.5%) (7). Additional descriptors include color heterogeneity, surface rugosity, presence of hypertrichosis, presence of dermal/subcutaneous nodules, and number of associated satellite lesions (9).

In a British cohort of 448 CMN patients aged 0-16 years, 10 (2.2%) developed melanoma, with a mean and median age at death from melanoma of 3.9 and 2.5 years, respectively. All 10 cases occurred in children with multiple CMNs, while 7 cases occurred in patients with a PAS >60 cm for the largest lesion (10). Nevertheless, melanoma risk estimates for patients with large or giant CMNs (LGCMNs) are imprecise, particularly due to significant biases of prior studies (e.g., relatively short length of follow-up, narrow age range for inclusion, or small sample sizes due to the disease's rarity) (11–14). Herein, we describe the case of a 30-year-old male with a childhood history of multiple excision/grafting procedures for a giant CMN who, more than 20 years later, developed an *NRAS*-mutant metastatic melanoma.

Case presentation

A 30-year-old Caucasian male, previously healthy, presented to the emergency department (ED) complaining of intermittent upper back pain. It started the previous evening while he was running and had a moderate intensity, stabbing quality, and radiation to the right chest. The patient denied any similar prior episodes, specific aggravating/alleviating factors, or associated acute-onset symptoms. On review of systems, he described a 12-lb weight loss over 3 months, besides having noted a painless, slow-growing right axillary lump for the previous 2 months. There were no additional constitutional symptoms, swelling of other areas (such as neck, inguinal region, or testicles), or easy bleeding/bruising. He also negated prior thromboembolic events, medication/hormonal use, or recent trauma, surgery, travels, infections, or sick contacts.

Past medical history was significant for a "birthmark" extending over his abdomen and lower back, for which multiple excision/grafting procedures were performed at 6 years of age.

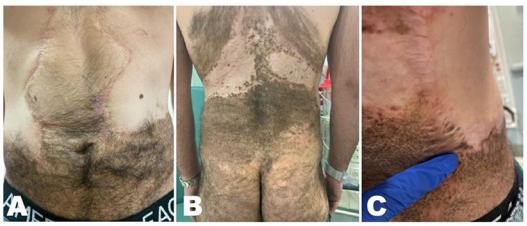

FIGURE 1
Heterogeneous brown-to-black patches and plaques with satellite lesions, areas of hypertrichosis and irregular borders, consistent with partially-excised giant congenital melanocytic nevus. **(A)** Scattered lesions over the lower abdomen. **(B)** Scattered lesions over the posterior thorax and buttocks. **(C)** Right mid-back nodular area where the initial incisional biopsy was performed.

He denied any itching, bleeding, or noticeable changes in the lesion's size, texture, color, or appearance for the last 20 years. The patient did not recall a specific diagnosis but reported consistent follow-up and mole mapping with a dermatologist outside the US. Despite being born in the UK, he lived in South Africa from early childhood until his 23 years of age and then returned to his home country, where he stayed until moving to the US a few months before presentation. When he was 10 years old, his father was treated for pulmonary tuberculosis. No other relevant family history was reported. He denied excess alcohol intake, current/former smoking, illicit drug use, overexposure to UV radiation, or known occupational hazards.

During bedside evaluation, the patient was found to have heterogeneous brown-to-black patches/plaques scattered on his torso, buttocks, and lower abdomen with satellite lesions, areas of hypertrichosis, and irregular borders, consistent with partially-excised giant CMN of bathing trunk distribution (Figure 1). The skin lesions were mostly flat except for a nodular border where grafting was previously done. In addition, a 2-cm mobile, firm, non-tender and non-erythematous subcutaneous nodule was palpated in the right axillary region. His physical exam was otherwise unremarkable.

On initial workup, blood counts, basic chemistries, liver function tests, troponin levels, urinalysis, and electrocardiogram were within normal limits. Conversely, serum D-dimer was elevated (2.42 mcg/mL) and chest radiography showed a left lower lobe (LLL) density of approximately 3 cm, leading to the acquisition of thoracic computed tomography (CT) angiography. Despite a lack of pulmonary emboli, significant findings included two LLL nodules (2.7 and 1.0 cm), a left posterior pleural-based nodule (0.8 cm), and a right lower lobe nodule (0.3 cm).

The patient was admitted to the hospital for further diagnostic evaluation. While serum lactate dehydrogenase (LDH) was elevated (350 U/L), other laboratory tests resulted

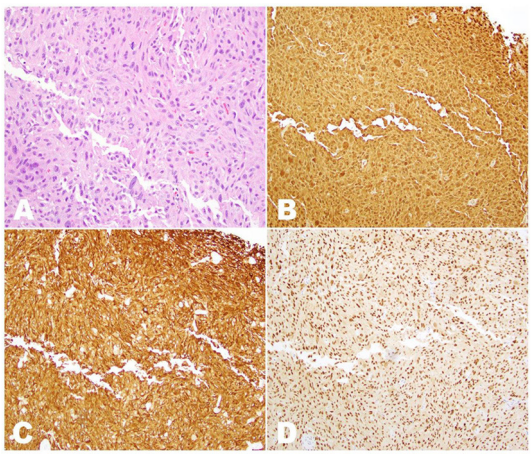

FIGURE 2
Histopathologic examination of the sample obtained by incisional biopsy of the right axillary nodule. **(A)** H&E stain (20× magnification), showing innumerous irregularly-shaped tumor cells with nuclear hyperchromasia and prominent nucleoli intermixed within fibroadipose tissue. **(B)** Immunostaining for S100 (10× magnification) showing diffuse nuclear and cytoplasmic positivity in all tumor cells. **(C)** Immunostaining for melan-A (10× magnification) showing diffuse cytoplasmic positivity in all tumor cells. **(D)** Immunostaining for PRAME (10× magnification) showing diffuse nuclear positivity in all tumor cells.

negative (including traditional tumor markers, hepatitis/HIV testing, QuantiFERON-TB Gold, and three sputum acid-fast bacillus smears). Contrast-enhanced CT (CECT) of the abdomen demonstrated hypodense lesions in the left and right adrenal glands (4.7 × 4.1 and 3.7 × 3.5 cm, respectively), between liver segments 2/3 (2.8 × 2.4 cm), and in the left inferior renal pole (1.4 × 1.1 cm). Brain magnetic resonance imaging (MRI) showed multiple enhancing parenchymal nodules of 0.4–1.2 cm, some of them with surrounding edema. Meanwhile, a whole spine MRI found no additional disease in the central nervous system (CNS) or vertebral bodies.

The high suspicion of metastatic cancer prompted an incisional biopsy of the right mid-back nodular area. Histopathological evaluation lacked evidence of malignancy and was consistent with reactive melanocytic proliferation to an underlying scar. As a result, the patient underwent an incisional biopsy of the right axillary nodule, with formalin-fixed paraffin-embedded (FFPE) samples revealing malignant cells within fibroadipose tissue (Figure 2). Immunohistochemistry (IHC) showed positivity for preferentially expressed antigen in melanoma (PRAME), S100, melan-A, and tyrosinase—a pattern consistent with melanoma—and negativity for *BRAF* V600E and *NRAS* Q61R. A hybridization capture-based next-generation sequencing assay (MSK-IMPACT) was also applied to the FFPE specimens. Although no microsatellite instability or structural variants were found, the tumor was positive for somatic mutations in *NRAS* exon 3 (c.181C>A, p.Q61K), *EP300* exon 31 (c.5992G>A, p.G1998R), and *MSH2* exon 12 (c.1996A>G, p.I666V). Additional findings included an estimated tumor mutation burden of 2.5 mutations/megabase and *MDM2*/*GLI1*/*ERBB3*/*CDK4*/*IGF1*/*TERT*/*SDHA*/*EP300*/*MSH2* amplification.

On account of his elevated serum LDH levels and CNS metastases, M1d(1) melanoma was ultimately diagnosed. As surgical metastasectomy was not appropriate, upfront treatment consisted of ipilimumab/nivolumab (3 mg/kg and 1 mg/kg, respectively, administered intravenously once every 3 weeks) and multifraction stereotactic radiosurgery of the brain (27 Gy divided into 3 daily fractions). Low-grade adverse events (hepatitis, thyroiditis, and oral mucositis) occurred after the first cycle of ipilimumab/nivolumab, but did not require immunotherapy discontinuation. Following 6 weeks of treatment, brain MRI showed interval contraction of CNS lesions and chest CTCE demonstrated stable pulmonary lesions. On the other hand, abdominopelvic imaging revealed new mesenteric/inguinal adenopathy and increased metastatic involvement of liver, kidneys, and adrenals.

The patient's rapid disease progression led to subsequent-line treatment with CVT (cisplatin 20 mg/m^2 IV on days 1–4, vinblastine 1.6 mg/m^2 IV on days 1–4, and temozolomide 150 mg/m^2 orally on days 1–5 administered every 21 days). Following 3 cycles of cytotoxic chemotherapy, CECT disclosed nonobstructing transient small bowel intussusceptions secondary to intra- and extraluminal metastatic lesions. As a result, the patient was transitioned to nivolumab/relatlimab (480 mg/160 mg IV once every 4 weeks). A few days after the second combination dose, he presented to the ED complaining of intractable abdominal pain. Repeat abdominal CECT showed an edematous, hypoattenuating closed-loop small bowel obstruction with twisting of the mesentery. Given the evidence of significant ischemia, exploratory laparotomy with partial small bowel resection and reanastomosis was performed. The patient recovered well, albeit with considerable weight loss related to continued anorexia and abdominal pain. Stable disease (<20% growth of target lesions) was observed after three nivolumab/relatlimab doses. However, interval imaging after the fourth dose showed progression of the thoracic and abdominopelvic masses. Figure 3 showcases a timeline with relevant data from the patient's clinical course.

Discussion

Progression to melanoma (cutaneous or extracutaneous) occurs in <1% of individuals with small or medium CMNs (10). In comparison, LGCMN patients have a 2.0–8.5% chance of malignant transformation (11, 12). Within this population, the probability of a lesion >20 cm evolving into cancer is not constant throughout life, with most evidence suggesting

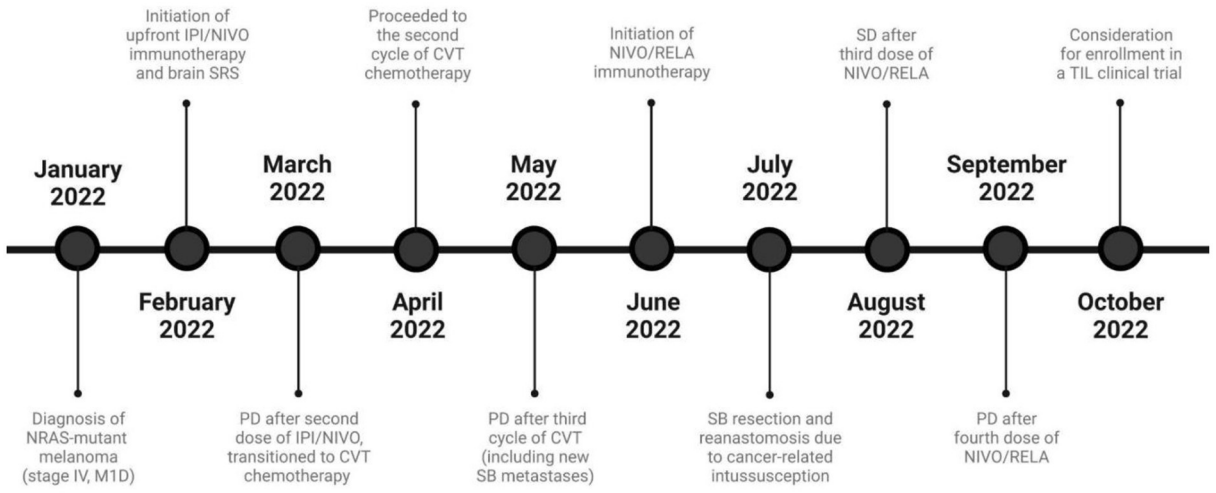

FIGURE 3
Timeline of the patient's clinical course and melanoma-directed therapy. CVT, Cisplatin/vinblastine/temozolomide; IPI, Ipilimumab; M1D, Metastasis to the central nervous system, with or without involvement of other sites; NIVO, Nivolumab; PD, Progressive disease; RELA, Relatlimab; SD, Stable disease; SB, Small bowel; TIL, Tumor-infiltrating lymphocytes.

an increased risk during early childhood (11–14). Noteworthy, melanoma is otherwise uncommon in children (0.032% of cases occur in individuals age 10 or younger) (13). Among LGCMN patients who develop melanoma, 50% are diagnosed within the first 5 years of life, with another 20% of cases being detected before puberty (13, 14).

In the above-described case, a 30-year-old male with a childhood history of a giant CMN was diagnosed with metastatic melanoma more than 20 years after partial nevus excision. This presentation is potentially rare, as LGCMN patients seem to experience a substantial decrease in their melanoma risk following pubertal onset (14–16). For instance, in a retrospective cohort of 379 LGCMN patients from 26 countries, the median and mean age at melanoma diagnosis were 3 and 8 years, respectively (15). Therefore, the present report highlights the continued risk of malignant transformation during adulthood for this population. Correspondingly, a few other similar cases have been described in the literature, including adults up to 70 years of age who also had undergone partial excision of their lesions (17–20).

Due to the low incidence of LGCMNs, current evidence on the appropriate management of the condition is somewhat scarce. Some clinicians defend an observation-only approach, with close monitoring for any signs of malignant transformation (e.g., color/size changes or nodularity). In contrast, others consider early surgical excision crucial to prevent progression to melanoma (11–14). Entirely excising LGCMNs remains a challenging task—nevus cells often aggregate in the reticular dermis, subcutis, and subfascial layers (e.g., deeper muscle and nerve structures), making complete excision very complex and often impossible (18, 21). Furthermore, the benefit on preventing malignant transformation seems to be limited—in a retrospective review of 950 patients with cosmetically-challenging CMNs (age 1.8–19.2 years at the time of last evaluation), no patients developed melanoma within small residual lesions (13). By analyzing histopathological changes over time in 21 CMN patients, Gassenmaier et al. (22) suggested that the lesion's cellularity and pigment production decrease with age, the histological pattern and extension in depth remain stable, and clear resection margins are rarely attainable in larger lesions.

In recent years, a paradigm shift on the long-term care and modern surgical treatment of CMNs has emerged, establishing the long-term aesthetic outcomes at the center of any therapeutic endeavor. According to CMN Surgery Network recommendations, adequate counseling on conservative and/or surgical management requires an interdisciplinary exchange among physicians and individualized planning of the intervention, which frequently involves a multi-stage procedure. Treatment-related adverse effects (e.g., hospitalization, impaired wound healing, and hypertrophic scarring) must be carefully weighed against the prospects of a beneficial outcome—for instance, dermabrasion has been often associated with cosmetically unfavorable results and considerable repigmentation rates (23). Although melanoma prevention plays only a minor role in management, the risk of malignant transformation seems to persist throughout the patient's life. In this scenario, the above-cited tendency of nevus cells to develop deep in the subcutaneous tissue (as well as in the CNS in the setting of neurocutaneous melanosis) can hinder malignancy detection at earlier stages. Moreover, LGCMN-related melanomas have a greater propensity toward

early metastases, as tumor cells are highly anaplastic (21). A reasonable way to deal with LGCMNs in adults could be lifetime monitoring with once-yearly dermatological examination (including lymph node palpation), despite a lack of prospective studies supporting this course of action (24, 25).

Further challenges are present after diagnosis, as molecular profiling varies widely (8). In a Chinese study, *BRAF* V600E mutations were not seen in LGCMNs, significantly contrasting with small and medium CMNs. Moreover, *BRAF* V600E never coexisted with *NRAS* exon 3 (codon 61) mutations in the same sample (26). In a Belgian series of 24 LGCMN patients, there was a high frequency of *NRAS* mutations (75% of cases) but *BRAF* mutations were less common (12% of cases) (27). Among the 19 LGCMN patients examined in a French study, 16 (84%) displayed an *NRAS* exon 3 (codon 61) mutation, while 1 carried a *BRAF* V600E mutation and 2 lacked alterations in those genes (28). In the present case, although IHC was negative to BRAF V600E and *NRAS* Q61R, subsequent molecular testing detected an *NRAS* Q61K mutation (seen in 34–50% of *NRAS*-mutant melanomas) (28, 29). Compared to other melanoma subtypes, *NRAS*-mutant tumors tend to be more aggressive and lead to worse outcomes (30, 31). For instance, our patient already had multiorgan metastases at the time of diagnosis, despite reporting few symptoms and no skin changes during initial evaluation.

Over the last decade, immune checkpoint inhibitors (ICIs) and targeted agents have significantly improved survival trends and response rates in BRAF-mutant melanoma. However, the ideal treatment for patients with *NRAS*-mutant melanoma remains unknown, especially due to the scarcity of prospective trials evaluating novel therapies in this patient subgroup (31, 32). Retrospective data has suggested that patients with *NRAS* mutations have higher response rates to immunotherapies, such as high-dose interleukin-2 and monoclonal antibodies (mAbs) against cytotoxic T-lymphocyte-associated protein 4 (CTLA4) or programmed cell death protein 1 (PD-1) (31–34). However, our patient responded poorly to first-line immunotherapy associating ipilimumab (anti-CTLA4 mAb) and nivolumab (anti-PD-1 mAb), developing rapid disease progression after 2 cycles. In the phase II Adaptively Dosed Immunotherapy (ADAPT-IT) trial, Postow et al. suggested that the efficacy of ipilimumab/nivolumab was driven by the first 2 combination doses, with patients being very unlikely to start responding after cycle 3 or 4 (35). From this perspective, our patient's treatment was switched to CVT, a multiagent cytotoxic regimen deemed well-tolerated and moderately efficacious in a phase II trial by the Hellenic Cooperative Oncology Group. In this study, subjects with BRAF-mutated tumors showed better response rates than those with BRAF wild-type tumors (39 vs. 27%), although subgroup analysis according to *NRAS* status was not performed (36). Ultimately, our patient's response to this line of therapy was poor. It is worth noting that little consensus exists regarding optimal standard chemotherapy for metastatic melanoma, which may reflect the low level of activity of older FDA-approved cytotoxic drugs and equivocal results from comparative phase III studies (37).

In March 2022, a fixed-dose combination of relatlimab—an anti-lymphocyte activation gene-3 (LAG-3) mAb—and nivolumab received FDA approval for advanced melanoma (38). This decision was based on the multinational, double-blinded, randomized phase II/III RELATIVITY-047 trial, which compared nivolumab/relatlimab vs. nivolumab monotherapy in 714 patients with newly-diagnosed metastatic or unresectable stage III/IV melanoma. After a median follow-up of 13.2 months, relatlimab's addition was associated with a significant increase in median progression-free survival (10.1 vs. 4.6 months; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.62–0.92; $P = 0.006$) (39). Correspondingly, the combined blockade of LAG-3 and PD-1 has been shown to promote synergistic effects in T-cell activation, causing enhanced antitumor activity compared to either alone (40).

MEK1/2 inhibition recently emerged as another therapeutic approach for *NRAS*-mutant melanoma (32, 37). In the phase III NEMO trial, binimetinib was associated with an overall response rate (ORR) of 15% and improved PFS compared with dacarbazine (2.8 vs. 1.5 months; HR, 0.62; 95% CI, 0.47–0.80; $P < 0.001$) (41). Thus, MEK inhibitors can be considered a useful option in patients with *NRAS*-mutant melanoma after failed immunotherapy. However, these agents are not widely available and further studies are needed to strengthen their incorporation into clinical practice (42). Although our patient had an MDM2 mutation detected, his CNS involvement deemed him ineligible for a clinical trial with an MDM2 inhibitor (NCT03611868) (43). Unfortunately, his molecular profiling did now show any additional targetable mutations that would allow management with other approved targeted drugs. Tumor-infiltrating lymphocyte (TIL) therapy as part of a clinical trial is a promising anti-melanoma strategy to be considered in patients with relapsed/refractory disease (44). In 2021, the phase 2 C-144-01 trial supported lifileucel's efficacy for advanced melanoma patients previously treated with ICIs and BRAF ± MEK targeted agents. Given the ORR of 36% (95% CI, 25–49) obtained with this agent (45), FDA approval is currently being sought. In addition to ongoing studies with lifileucel, novel TIL products are being actively investigated in multicentric trials (NCT05050006, NCT03997474) (44).

Conclusion

This report highlights the importance of lifetime monitoring for progression to melanoma in large/giant CMN patients, regardless of whether partial/complete excision was performed. Although previous cohorts suggest that most malignant transformations occur during childhood, adults with a history of large/giant CMNs remain at a significantly higher risk of developing melanoma than the general population. As

illustrated by the present case, melanomas associated with large/giant CMNs often harbor *NRAS* mutations—a biomarker of disease aggressiveness and worse clinical outcomes. Given that the ideal management for patients with *NRAS*-mutant melanoma remains unknown, further clinical studies are urgently needed to improve their prognosis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BC, AB, VZ, and VS conceived and designed the study. BC, VZ, SG, AM, OH, and AB collected, analyzed, and interpreted clinical data. BC, VZ, SG, and AM wrote the first draft of the manuscript. VS, OH, and AB critically reviewed the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Conflict of interest

Author OH: Consulting: Aduro, Akeso, Amgen, Beigene, Bioatla, BMS, Roche Genentech, GSK, Immunocore, Idera, Incyte, Janssen, Merck, Nextcure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Tempus, Zelluna; Speakers Bureau: BMS, Novartis, Pfizer, Sanofi/Regeneron; Research Funding Institutional: Arcus, Aduro, Akeso, Amgen, Bioatla, BMS, CytomX, Exelixis, Roche Genentech, GSK, Immunocore, Idera, Incyte, Iovance, Merck, Moderna, Merck-Serono, NextCure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Torque, Zelluna. Author AB: Consulting: Iovance Biotherapeutics, BluePath Solutions, Nanobiotix, Novartis, Pfzer; Honoraria: Shanghai Jo'Ann Medical Technology; Research Funding Institutional: Iovance Biotherapeutics, Leap Therapeutics, Daiichi Sankyo.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Case Report
PUBLISHED 08 December 2022
DOI 10.3389/fmed.2022.1055045

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 27 September 2022
ACCEPTED 21 November 2022
PUBLISHED 08 December 2022

CITATION
Moro F, Mariotti F, Pira A, De Luca N, Didona B, Pagnanelli G and Di Zenzo G (2022) Case report: Bullous pemphigoid arising in a patient with scleroderma and multiple sclerosis.
Front. Med. 9:1055045.
doi: 10.3389/fmed.2022.1055045

Case report: Bullous pemphigoid arising in a patient with scleroderma and multiple sclerosis

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Background: Bullous pemphigoid (BP) is the most common autoimmune-blistering disease, clinically characterized by erythematous urticarial plaques, blisters, and intense pruritus, induced by autoantibodies against two proteins of the dermo-epidermal junction, BP180 and BP230. A large number of autoimmune diseases are reported in the literature as BP comorbidities, such as multiple sclerosis, but only a few cases are in association with scleroderma and none in association with both.

Case presentation: We present the case of a 68-year-old woman affected by multiple sclerosis and scleroderma who developed severe bullous pemphigoid with a bullous pemphigoid disease area index of 60 and high titers of anti-BP180 and anti-BP230 autoantibodies by enzyme-linked immunosorbent assays. After 2 months of therapy with both intravenous and oral corticosteroids, the active lesions of bullous pemphigoid were remitted with no relapse.

Conclusion: Autoimmune diseases affecting the skin or organs where BP180 and BP230 are present could trigger an immune response to these antigens through an epitope-spreading phenomenon and, over the years, induce bullous pemphigoid onset.

KEYWORDS

bullous pemphigoid, scleroderma, multiple sclerosis, BP180, BP230

Introduction

Bullous pemphigoid (BP) is the most common autoimmune-blistering disease, induced by autoantibodies against two proteins of the dermo-epidermal junction, BP180 and BP230. The binding of the autoantibodies results in an inflammatory response with complement activation, degranulation of mast cells, accumulation of neutrophils and eosinophils, and release of proteolytic enzymes that cleave BP180 and lead to blister formation. Clinically, BP is characterized by intense pruritus, erythematous urticarial plaques, and blisters. The diagnostic gold standard is the confirmation with direct immunofluorescence (DIF) of linear deposition of IgG and/or C3 along the dermo-epidermal junction. Other useful assays are indirect immunofluorescence to reveal IgG staining of the dermo-epidermal junction, enzyme-linked immunosorbent assays (ELISA) to detect autoantibodies against BP180 and BP230, and the histological examination of lesional skin biopsy to evaluate dermo-epidermal detachment and inflammatory infiltrate. A large number of autoimmune diseases are reported in the literature as BP comorbidities: psoriasis, rheumatoid arthritis, lupus erythematosus, lichen planus, membranous nephropathy, pernicious anemia, primary biliary cirrhosis, thyroiditis, polymyositis, and multiple sclerosis (MS) (1, 2). On the other hand, only a few cases of BP associated with connective tissue disorders, such as systemic sclerosis, also termed scleroderma (SCL) (two cases) or morphea (three cases), are reported, and no case of BP has been described in association with both MS and SCL, so far (3–7).

Case description

In February 2022, a 68-year-old woman came to our clinic for evaluation of bullous and urticarial lesions. On physical examination, the patient showed excoriations and tense bullae on an inflammatory basis in the upper limbs, lower limbs, trunk, and abdomen and a lesion in the nasal mucosa, with a bullous pemphigoid disease area index (BPDAI) score of 60 (**Figure 1A**). She also showed sclerodactyly with Raynaud's phenomenon, tightening facial skin with telangiectasias, thin lips, and perioral wrinkles. At physical examination, no other remarkable sign was detected. She had no family history of autoimmune-blistering disease or different skin inflammatory diseases. The findings of routine laboratory tests, chest radiography, and abdominal computed tomography scan were within normal limits.

The patient reports that bullous lesions started in October 2021 in a milder form, and she initially went to a private practice dermatologist who set therapy with betamethasone 5 mg/day (**Figure 2**). The lesions remitted during the treatment and then relapsed in a more severe form with an unbearable itching in the trunk and limbs once the intake of corticosteroids was stopped.

Medical history has revealed that the patient is also affected by MS, diagnosed in 1988 following 14 episodes of optic neuritis: magnetic resonance imaging and lumbar puncture showing oligoclonal bands confirmed the diagnosis (**Figure 2**). She was treated from 1991 to 2001 with interferon alfa and subsequently from 2001 to 2006 with Glatiramer acetate 20 mg/die thrice per week. Thereafter, she underwent only oral or intravenous corticosteroids. Since 2011, the MS has been in clinical control, and the patient does not use any medication.

In addition, in 2007, the patient was evaluated for Raynaud's phenomenon and skin thickening in both hands. Capillaroscopy revealed vascular anomalies, such as mega capillaries and avascular areas (**Figure 2**). Subsequent blood tests showed positivity for ANA and Scl-70 antibodies. The diagnosis of SCL was set, though the computed tomography scan was negative for other organ damage, and therapy with nifedipine and oral corticosteroids 10 mg/die was set up. After 5 years, the treatment was suspended because the disease was considered not active.

We decided to hospitalize the patient, and a blood draw and skin biopsy were performed. Histological examination showed a subepidermal detachment, with inflammatory infiltrate of neutrophils and eosinophils. DIF was positive with linear deposition of IgG and C3 along the dermo-epidermal junction (**Figure 1B**). We performed indirect immunofluorescence on human salt-split skin and BP180 and BP230 ELISAs. Both the immunological assays resulted in positive with IgG staining of the epidermal side of the artificial blister by IIF (**Figure 1C**) and IgG titers of 36.4 and 44.1 U/ml against BP180 and BP230, respectively (negative <9 U/ml for both BP180 and BP230 ELISA) (MBL, Nagoya, Japan).

The laboratory data, the biopsy outcome, and the suggestive clinic features allowed us to diagnose BP. Of note, at the time of the BP diagnosis, the patient was not receiving medication for MS and SCL or other diseases.

We decided on therapy with intravenous corticosteroids and methylprednisolone 40 mg/day for 7 days. After 7 days, the patient's BPDAI dropped to 33 with no new lesions reaching disease activity control.

The patient left the hospital and continued to take oral prednisone at a dosage of 25 mg/day and to use topical therapy (Clobetasol propionate 0.05% cream) twice a day on lesions. No other steroid-sparing medication was used. After 2 months, she reached remission on minimal therapy of 10 mg/day of prednisone, and a BPDAI of 10 was only obtained with damage evaluation (**Figure 1D**). Two months later, she was in complete remission at 5 mg/day of prednisone with a BPDAI of 3. In the present case, the prompt response to therapy could be related to the absence of comorbidities and good general condition. The patient reported no problems returning to regular daily activity, with no physical or psychological sequelae since she reached remission on minimal therapy.

10.3389/fmed.2022.1055045

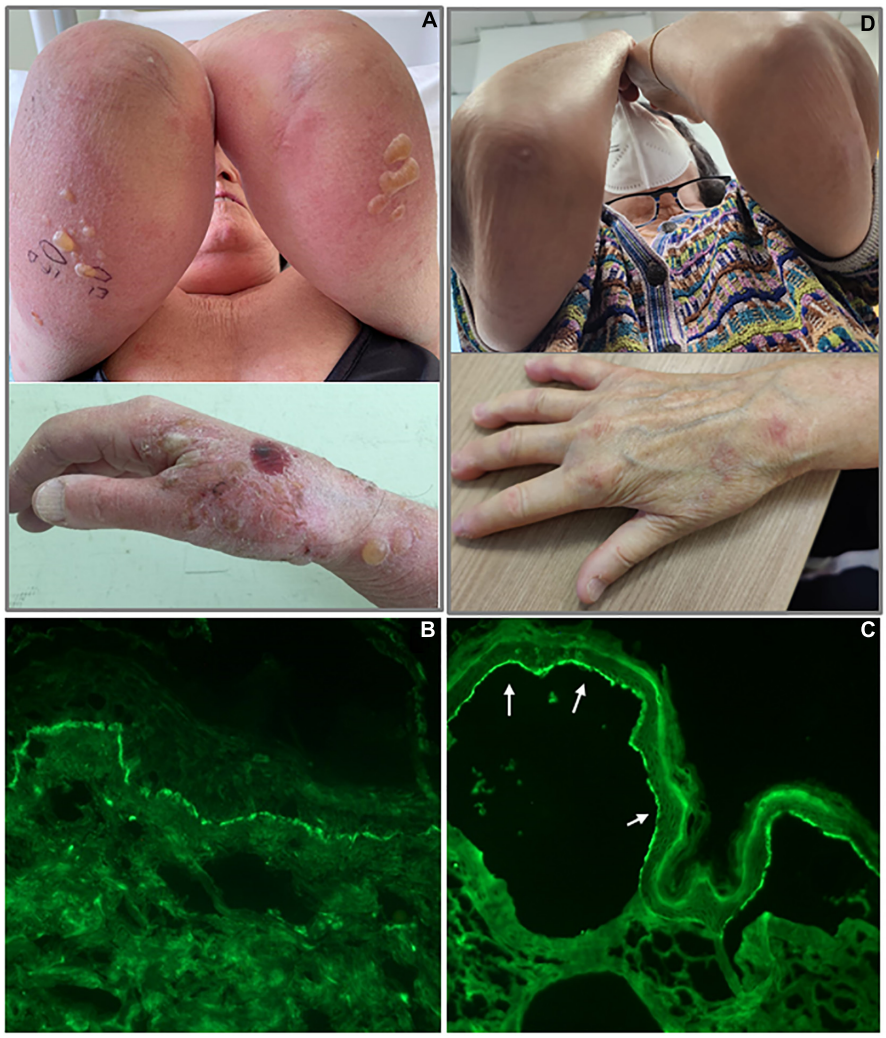

FIGURE 1
Clinical and immunological findings of bullous pemphigoid patient. **(A)** Tense bullae in the upper limbs and the right hand; **(B)** linear deposition of IgG along the dermo-epidermal junction by direct immunofluorescence; **(C)** IgG staining of the epidermal side (white arrows) of the artificial blister by indirect immunofluorescence on human salt-split skin; and **(D)** patient with BP in complete remission on minimal therapy.

Discussion

We presented a case of BP arising in a patient affected by two different systemic autoimmune diseases. MS is a demyelinating autoimmune disease that has been associated with the onset of BP in various studies (8, 9). A recent meta-analysis defined a relative risk of MS among patients with BP of 12.40 (2). The mechanism behind this association remains unknown. It has been found that the genes of BP target antigens are expressed in the central nervous system, so it has been assumed that repeated insults to the organ can induce an epitope-spreading phenomenon and trigger an autoimmune response in predisposed individuals. Several studies are needed to elucidate this mechanism better.

The SCL is a rare autoimmune connective tissue disorder presenting with cutaneous sclerosis and systemic involvement, while morphea is a localized scleroderma confined to the skin and/or underlying tissues. A few cases of BP associated with SCL or morphea have been described in the past. In most reported cases, the association appears to be occasional, often explained as a consequence of Koebner's phenomenon or as an association/adverse effect following drug therapy. Therefore, given the small number of cases and other factors that could intervene, the association was considered causal (5–7). More recently, Cozzani et al. also reported a BP occurring in a patient with SCL. However, the patient had recently taken piperacillin and, according to the Naranjo algorithm, the diagnosis was consistent with drug-induced BP (4). In 2022, Maglie et al.

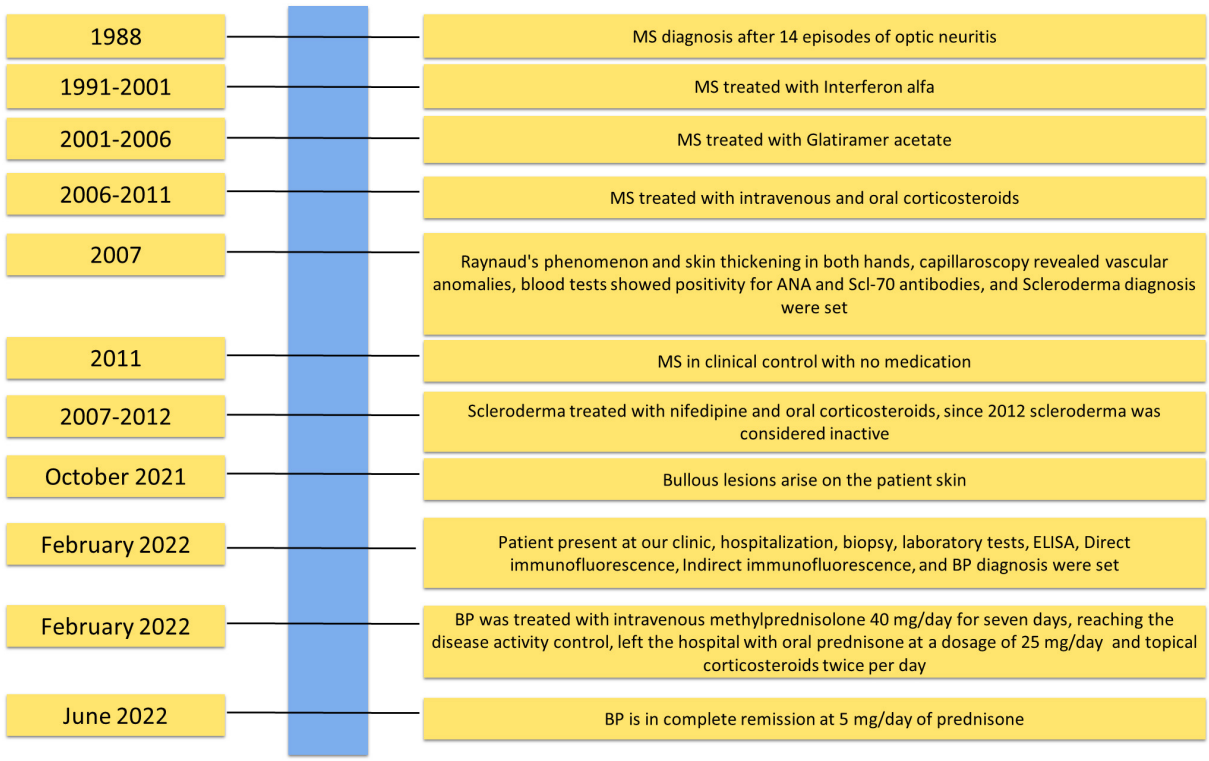

FIGURE 2
Timeline with relevant data about the onset, diagnosis, and therapy of bullous pemphigoid patient.

reported a case of BP in a patient with a long history of morphea and lichen sclerosus. Interestingly, they report the BP lesions were localized to the same area previously affected by morphea and lichen sclerosus. The authors hypothesized that morphea and lichen sclerosus could be two predisposing factors for the development of BP due to a T-cell reactivity to BP180 NC16A and a Th2-type signaling activation (3).

In our patient, BP developed 34 years after the diagnosis of MS and 14 years after the diagnosis of SCL. In the absence of other events that may have acted as trigger factors, such as drug intake, trauma, radiation, recent infections, and UV exposure, we can hypothesize that the two pre-existing autoimmune diseases acted as predisposing factors. In general, the impairment of the immune system based on MS and SCL could provide the immunological background for the induction of BP. In addition, the autoimmune response could lead to chronic tissue damage inducing the activation and recruitment of lymphocytes specific for epitopes/antigens, which are distinct from and non-cross-reactive with the disease-inducing epitope/antigen. In this context, one of the target tissues for SCL is the skin, where BP antigens, BP180 and BP230, are structural components. In parallel, in MS, the target of an autoimmune response is the central nervous system, where BP180 and BP230 expressions have been demonstrated (10–12). In addition, anti-BP180 and anti-BP230 autoantibodies were detected in the cerebrospinal fluid of patients with BP and neurological diseases (13). Immunosenescence may have a role in the development of BP, and in our case, it may have been a crucial trigger factor (1). However, not all aged patients affected by MS and/or SCL develop BP, suggesting that other specific predisposing factors are needed. It could be hypothesized that the pre-existence of low titers of circulating autoantibodies arising after chronic exposure to antigens may have favored BP development in our aged patient.

The strength of our case is the unicity; as we know, this is the first reported case of MS, scleroderma, and BP arising in the same patient. As for the limitations, we do not have a blood sample before the BP onset, and we cannot state the presence of low-titer autoantibodies before the clinical presentation.

Conclusion

This case could lead to thinking that autoimmune diseases affecting the skin or organs where genes coding for BP180 and BP230 are expressed could, over time, induce the exposure of antigens, stimulate a specific activation of the immune system, and consequently lead to the development of BP.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Istituto Dermopatico dell'Immacolata (IDI) IRCCS. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

GD, GP, and BD conceived and design the study. GD and FMo wrote the manuscript. FMa, AP, and ND collected the data and performed the analysis and experiments. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the "Progetto Ricerca Corrente" and "Ricerca Finalizzata" (N 12367807) of the Italian Ministry of Health, Rome, Italy.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Case Report
PUBLISHED 07 February 2023
DOI 10.3389/fmed.2023.1049477

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 20 September 2022
ACCEPTED 03 January 2023
PUBLISHED 07 February 2023

CITATION
Albert E, Walsemann T, Behrends J and Jappe U (2023) Lipid transfer protein syndrome in a Northern European patient: An unusual case report.
Front. Med. 10:1049477.
doi: 10.3389/fmed.2023.1049477

Lipid transfer protein syndrome in a Northern European patient: An unusual case report

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Non-specific lipid transfer proteins (nsLTPs) as the primary sensitizer in plant-food allergic patients used to be seen primarily in the Mediterranean area. However, more recently, increasing numbers of clinically relevant sensitizations are being observed in Northern Europe. We herein report an unusual case of a woman who developed an anaphylactic reaction during a meal including a variety of different foods ranging from fruits and nuts to oats, wheat, and salmon. Allergy diagnostics showed no Bet v 1 sensitization but an nsLTP-mediated food allergy. Despite the much more prominent birch food syndrome in Central and Northern Europe, LTPs should be considered disease-causing agents, especially for patients developing severe reactions after consuming LTP-containing foods.

KEYWORDS

non-specific lipid transfer protein, LTP, LTP syndrome, food allergy, basophil activation test, exercise-induced anaphylaxis

Introduction

Non-specific lipid transfer proteins (nsLTPs) are small, highly structurally stable proteins found in various plant foods and pollen. Their structure contains four disulfide bonds that are responsible for their resistance to thermal processing as well as gastrointestinal digestion (1). These characteristics provide them with the ability to induce primary gastrointestinal sensitization. LTPs as a major cause of food allergy have so far been mainly recognized in the Mediterranean area, while reports of LTP-mediated food allergy in Northern Europe have been rare (2). In this area, the birch food syndrome is the dominant cause of allergic reactions to various plant foods, whereas LTPs as the cause of pollen-associated or primary food allergy still seem to be rare (2). Patients with birch food syndrome sometimes simultaneously present with co-sensitization to LTPs like Pru p 3 (peach), Cor a 8 (hazelnut), Mal d 3 (apple), and others, but these cases mostly show mild allergic reactions (3). In contrast to that, LTP-mediated food allergy often presents with much more severe manifestations (4). Patients with LTP syndrome experience reactions to multiple plant foods due to the wide distribution of these allergens in plant sources (5). The severity of reactions additionally increases with the number of LTP sensitizations (2). In some cases, the manifestation of symptoms in allergic patients can depend on the presence of a cofactor, such as exercise (6). These cofactors potentially amplify allergic

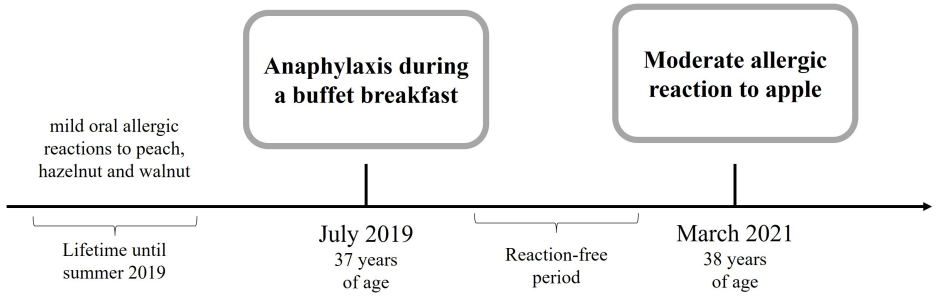

FIGURE 1
Timeline of the patient's allergological history.

reactions by decreasing the amount of allergen needed to induce reactions in patients with lower allergen sensitization (7). Currently, the understanding of the pathomechanism behind this phenomenon remains to be fully understood. One proposed mechanism behind exercise-induced anaphylaxis involves changes in the mucosal permeability resulting in increased allergen exposure (7). We herein describe the case of a woman who developed two separate allergic reactions after consumption of plant foods, the first one presenting as anaphylaxis and the second one as an oral allergy syndrome. In the case of the anaphylactic reaction, the cofactor exercise was present before consumption. Allergy diagnostics revealed evidence of an LTP-mediated food allergy.

Case description

A 37-year-old woman presented to the emergency department with an anaphylactic shock including burning and tingling of her tongue, emesis and diarrhea, generalized urticaria, facial angioedema progressing to dizziness, and difficulties in swallowing and breathing due to swelling of her throat. Her past medical history included lactose intolerance and sensitization to house dust mites, and she also experienced non-allergy related diseases including Hashimoto's thyroiditis and autoimmune uveitis. The patient neither suffered from allergic rhinitis, asthma, or atopic eczema nor did she take any medication regularly. This anaphylactic reaction happened during a buffet breakfast with a multitude of allergen sources including salmon, pine nuts, walnuts, sesame, wheat, oats, mustard, honey, orange juice, melon, apple, grapes, grapefruit, blood orange, and coffee. Thorough clinical history revealed that the patient underwent physical exercise 60 min before her breakfast. She remained incident-free for more than one and a half years until she presented a second time to a primary care physician with an intense tingling of the tongue after consumption of an apple crumble and coffee (**Figure 1**). No other LTP-containing foods were consumed in parallel. Almost all the ingredients of the apple crumble she had been eating daily, besides the apple itself, which is why the apple was considered suspicious of being the allergy trigger. This time physical activity as a cofactor was excluded; however, menses and the intake of non-steroidal antiphlogistics are probable. Medical history further revealed that the patient had experienced itchy eyes, an erythematous itchy reaction at her neck, and swelling of her lips after the consumption of peach many years ago, which was her very first allergic reaction. The consumption of walnut and hazelnut was accompanied by oral allergy syndrome, and in the case of hazelnut (hazelnut flour in a bread roll), the eyes were itchy and the lips were swollen in addition to oral allergy syndrome.

Diagnostic assessment

Diagnostic assessment: skin prick testing revealed sensitization to peach (3 mm) and hazelnut (5 mm). Herring, hen's egg extract, crab extract, peanut extract, walnut, almond, cow's milk, soya milk, wheat flour, lupine flour, raw apple, raw carrot, raw celery, and raw tomato were negative. The positive control (histamine) reaction was 5 mm. The concentration of specific IgE-antibodies to different allergen extracts and single allergens was determined by Immuno Solid-phase Allergen Chip (ImmunoCAP; Phadia; Uppsala, Sweden). Total serum IgE was slightly elevated (110 kU/L; normal <100 kU/L). Specific IgE (sIgE) to allergen extracts was positive for pine nut, lupine seed, mugwort, olive tree, *Dermatophagoides farinae*, and *D. pteronyssinus*, and negative (<0.01 kU/L) for wheat and mustard. Specific IgE to single allergens was positive in descending concentration for the nsLTPs of peach (rPru p 3), apple (rMal d 3), mugwort (n Art v 3), walnut (rJug r 3), rAra h 9, wheat (rTri a 14), hazelnut (rCor a 8), and the olive tree (r Ole e 7). These results are shown in **Table 1**. The detailed medical history led to the suspicion of an LTP-mediated reaction to food. This suspicion was confirmed by *in vitro* allergy diagnostics showing no IgE reaction toward birch pollen [Bet v 1, Bet v 2 (profilin), and Bet v 4 (polcalcin)] but positive reactions to multiple lipid transfer proteins (**Table 1**). In addition to specific IgE detection, a basophil activation test (BAT) with the lipid transfer proteins from lupine (*Lupinus luteus*, originates from the research group Prof. Jappe) (**Figure 2A**) and from wheat, peanut, peach, and hazelnut (Indoor Biotechnologies Ltd., Cardiff, UK) (**Figure 2B**) was performed, which revealed a positive result for peach, lupine, and peanut in descending order and was negative for wheat and hazelnut. The LTPs from apple and pollen were not included as they were not available for BAT. There were no IgE reactions in ImmunoCAP to the peanut storage proteins Ara h 1–3 and Ara h 8, the Bet v 1-homolog in peanut, so the reaction to lupine LTP is most probably a cross-reactivity between LTPs. With sIgE of five or more LTPs, reactions are usually severe, leading to the diagnosis of LTP syndrome in this patient. The patient was advised to avoid the consumption of apples in any form and was equipped with an emergency set consisting of an adrenaline auto-injector,

TABLE 1 *In vitro* allergy diagnostics: Specific IgE-antibody detection results (ImmunoCAP).

Allergen source	Protein family/ biochemical name	Allergen component	IgE (kU/L)	CAP class
Peach (*Prunus persica*)	**nsLTP**	**rPru p 3**	8.7	3
Peach (*Prunus persica*)	Bet v 1-homolog	rPru p 1	0.13	0
Peach (*Prunus persica*)	Profilin	rPru p 4	< 0.01	0
Peach (*Prunus persica*)	Gibberellin-regulated protein	rPru p 7	< 0.01	0
Apple (*Malus domestica*)		Extract	4.5	3
Apple (*Malus domestica*)	nsLTP	**rMal d 3**	7.97	3
Apple (*Malus domestica*)	Bet v 1-homolog	rMal d 1	< 0.01	0
Walnut (*Juglans regia*)		Extract	3.22	2
Walnut (*Juglans regia*)	nsLTP	**rJug r 3**	3.22	2
Walnut (*Juglans regia*)	2S albumin	rJug r 1	< 0.01	0
Lupine seed (*Lupinus albus*)		Lupine seed extract	2.3	2
Wheat (*Triticum aestivum*)	nsLTP	**rTri a 14**	1.63	2
Wheat (*Tr. aestivum*)	Omega-5 gliadin	rTri a 19	< 0.01	0
Wheat (*Triticum aestivum*)		Wheat extract	< 0.01	0
Pine nut		Pine nut extract	1.25	2
Hazelnut (*Corylus avellana*)	nsLTP	**rCor a 8**	0.66	1
Hazelnut (*C. avellana*)	11S seed storage globulin	rCor a 9	< 0.01	0
Hazelnut (*C. avellana*)	2S albumin	rCor a 14	< 0.01	0
Peanut (*Arachis hypogaea*)	nsLTP	**rAra h 9**	3.72	2
Peanut (*A. hypogaea*)		Extract	1.21	1
Peanut (*Arachis hypogaea*)	7S globulin	rAra h 1	< 0.01	0
Peanut (*Arachis hypogaea*)	2S albumin	rAra h 2	< 0.01	0
Peanut (*Arachis hypogaea*)	11S globulin	rAra h 3	< 0.01	0
Peanut (*Arachis hypogaea*)	Bet v 1-homolog	rAra h 8	< 0.01	0
Mustard		Mustard extract	< 0.01	0
Mugwort		Mugwort extract	2.08	2
Mugwort	nsLTP	**nArt v 3**	4.08	3
Olive tree (*Olea europaea*)		Olive tree extract	0.18	0
Olive tree	nsLTP	**rOle e 7**	0.69	1
Pellitory (*P. juglans*)		Extract	< 0.01	0
Parietaria juglans	nsLTP	**rPar j 2**	< 0.01	0
Birch pollen (*Betula verrucosa*)	PR 10-Protein	rBet v 1	0.17	0
Birch pollen (*Betula verrucosa*)	Profilin	rBet v 2	< 0.01	0
Birch pollen (*Betula verrucosa*)	Polcalcin	rBet v 4	< 0.01	0
Timothy (*Phleum pratense*)	Polcalcin	rPhl p 7	< 0.01	0
Timothy (*Phleum pratense*)	Profilin	rPhl p 12	< 0.01	0

glucocorticosteroids, and antihistamines. There has been no re-presentation since.

Discussion

Outside the Mediterranean area, LTP-mediated allergic reactions remain a rare diagnosis, and a full understanding of these geographical differences is still to be developed. Northern European countries have a higher load of birch pollen in comparison to Mediterranean countries. This high load of birch pollen with the dominance of Bet v 1 as a major allergen and primary sensitizer is suspected to decrease the probability of primary sensitizations to lipid transfer proteins in pollen, leading to mostly mild allergic reactions in LTP-sensitized Northern European patients (8). In contrast to that, LTP-mediated allergy can provoke various and more severe symptoms, including urticaria, nausea, diarrhea, angioedema,

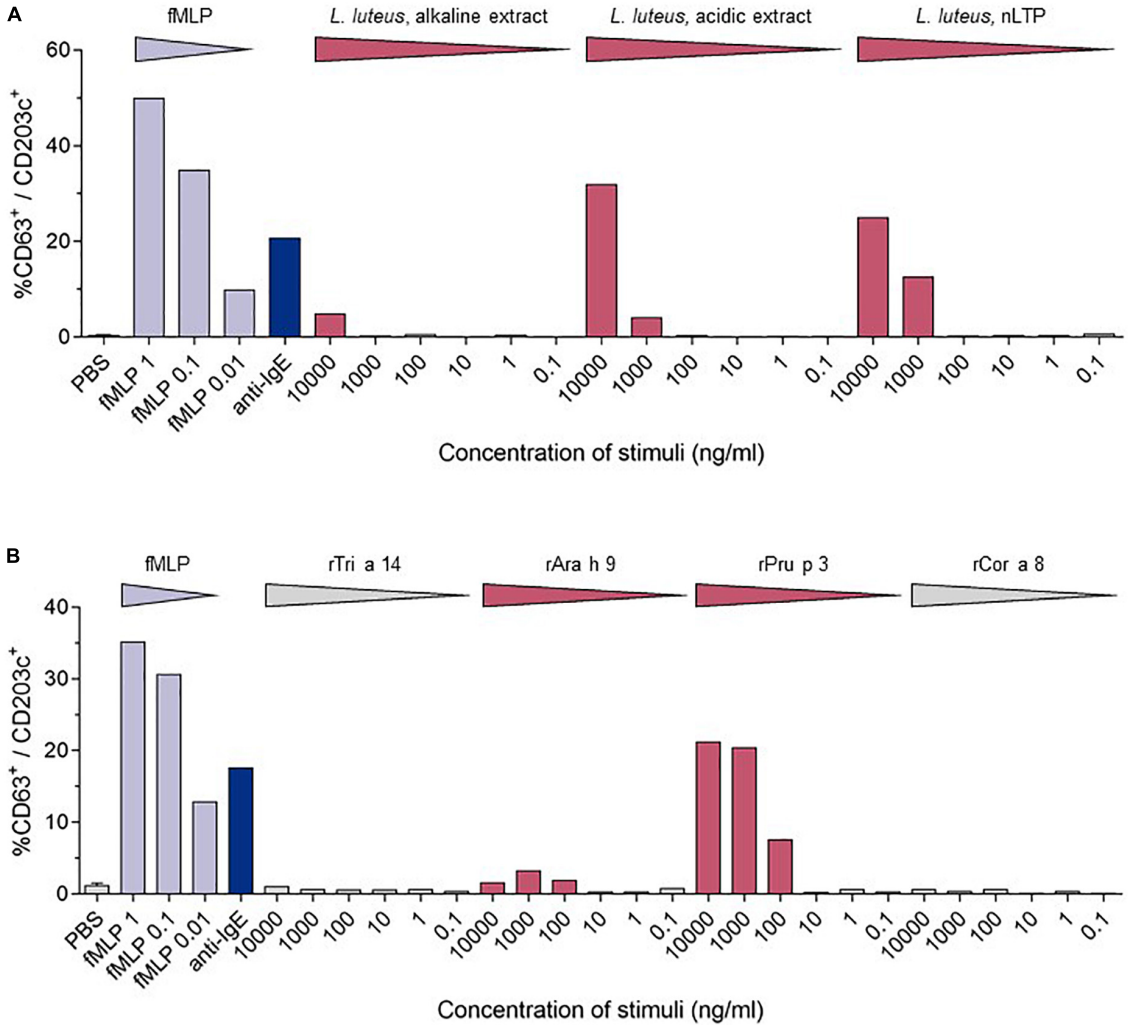

FIGURE 2
Comparison of the stimulation-induced basophil activation levels. Basophil activation was measured by the percentages of CD63 positive basophils ($CD203c^+/Fc\epsilon RI\alpha^+$). PBS—phosphate-buffered saline, fmlP- formyl-, methionyl-leucyl phenylalanine. **(A)** Results of the BAT for LTPs from *Lupinus luteus* [acidic extract; alkaline extract; nLup l 3 (LTP)] (10). **(B)** BAT results from wheat (rTri a 14), peanut (rAra h 9), peach (rPru p3), and hazelnut (rCor a 8).

dizziness and even swelling of the throat, dyspnea, as well as cardiovascular disruptions. In our case, LTP-mediated anaphylaxis was induced by the consumption of multiple LTP-containing foods with preceding physical activity as a cofactor. The absence of typical birch pollen allergy symptoms like allergic rhinitis combined with the missing Bet v 1 sensitization led to the exclusion of the diagnosis of a birch pollen food syndrome. Our patient showed a strong sensitization to peach (rPru p 3), apple (rMal d 3), a moderate sensitization to walnut (rJug r 3) and wheat (rTri a 14) nsLTPs, as well as a low sensitization to the hazelnut nsLTP (rCor a 8). For peach, walnut, and hazelnut, the patient reported previous mild allergic reactions, which according to ImmunoCAP-results are not based on Bet v 1 or panallergens like profilins and polcalcins, but LTPs. The skin prick test and IgE-antibody assays can only detect sensitization and do not provide proof of allergy (9). The basophil activation test mimics the allergic reactions *in vitro*, and after optimization, discriminates between peanut-allergic and -sensitized individuals (9). For this patient, the BAT was performed using lupine, which is a legume like peanut, and the lipid transfer protein from yellow lupine seeds (nLup l 3), which was first identified and purified by Jappe et al. (10), and was, therefore, the original part of the "tool box" of the research group. After having obtained a positive reaction in BAT as proof-of-principle, additional commercially available LTPs (rTri a 14, rAra h 9, rPru p 3, and rCor a 8) were used in BAT. Although lupine seeds or lupine products were not knowingly a part of the buffet breakfast and the cross-reactive legume peanut is consumed daily without symptoms, this result together with the strong reaction to Pru p 3 and additional weaker reaction to Ara h 9 supports the diagnosis "LTP syndrome" in which patients are polysensitized to multiple LTPs from different food sources (1). During the anaphylactic event, the patient consumed multiple LTP-containing foods. None of them were identified as a new food source for the patient, which is why it is unlikely that anaphylaxis was induced by a single newly introduced allergen/allergen source. We propose it to be more likely that physical activity might have decreased the threshold of allergy induction. That, in combination with a high load of consumed LTP-containing foods, has potentially led to the severity of her reaction. This hypothesis of the LTP amount consumed as a risk factor in our patient is supported by the fact that the patient has not suffered a comparable allergic reaction before. The hypothesis is

also supported by a recently published study on 67 Spanish patients with LTP-related anaphylaxis, 55/67 with anaphylaxis and a total of 134 anaphylactic reactions and 12/67 with anaphylactic shock and a total of 16 reactions (11). Another aspect in question is the route of sensitization. Possible routes include sensitization through cutaneous, gastrointestinal, and inhalant exposure (1). Asero reported peach-induced contact urticaria showing an association with nsLTPs (12). Primary gastrointestinal sensitization is a common cause of food allergy. For Pru p 3, Tordesillas et al. showed that it crosses the gastric barrier, which could be a reason for primary sensitization *via* the gastric route (13). Reactions to plant food sources can also occur *via* the inhalant route. One example is the birch-food syndrome describing cross-reactivity to vegetables and fruits containing Bet v 1-like proteins. Other inhalant allergen sources contain nsLTPs, which could lead to sensitization to nsLTPs *via* the inhalant route (14). Pollen nsLTPs like Ole e 7 from the olive tree, Art v 3 from mugwort, and Pla a 3 from the plane tree share partial cross-reactivity with *Rosaceae* nsLTPs and could be responsible for primary sensitization (15). As mugwort is especially common also in Northern Europe, we tested for the respective specific IgE-antibodies. The patient was indeed sensitized to the mugwort nsLTP nArt v 3. The patient originates from Northern Germany. There were no journeys to the Mediterranean area longer than 2 weeks. As the IgE concentrations to inhalant allergen sources and their LTPs were considerably lower than for peach and apple LTPs, we assume that the sensitization has most probably occurred *via* the ingestion of peach (see the first allergic reaction she has ever experienced.). This assumption is supported by the dominant sensitization to rPru p 3 in ImmunoCAP and the strong reaction to rPru p 3 in the BAT.

Conclusion

An LTP-mediated allergy can provoke potentially life-threatening allergic reactions. Despite the much more prominent birch food syndrome in Central and Northern Europe, LTP allergens should be considered disease-causing agents and included in allergy diagnostic tests, especially for patients who experience severe reactions after consuming LTP-containing foods.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

EA wrote the manuscript and designed the **Figure 1**. TW planned, measured and analyzed BAT experiments and data, and designed the **Figure 2**. JB measured and analyzed BAT experiment and data. UJ diagnosed the patient, wrote and obtained ethical approval, wrote and revised the manuscript, and wrote the **Table 1**. All authors approved the final version of the manuscript.

Acknowledgments

We wish to express our gratitude to Daniel Rosero for his excellent technical support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 28 March 2023
DOI 10.3389/fmed.2023.1132574

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 27 December 2022
ACCEPTED 06 March 2023
PUBLISHED 28 March 2023

CITATION
Yu Y, Ding X, Guo F, Ze K, Sun X and Li X (2023) Perifolliculitis capitis abscedens et suffodiens treatment with tumor necrosis factor inhibitors and baricitinib: A case report and literature review.
Front. Med. 10:1132574.
doi: 10.3389/fmed.2023.1132574

Perifolliculitis capitis abscedens et suffodiens treatment with tumor necrosis factor inhibitors and baricitinib: A case report and literature review

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Rationale: Perifolliculitis capitis abscedens et suffodiens (PCAS), also known as dissecting cellulitis of the scalp (DCS), is a part of the "follicular occlusion tetrad" that also includes acne conglobate (AC), hidradenitis suppurativa (HS), and pilonidal sinus, which share the same pathogenic mechanism, such as follicular occlusions, follicular ruptures, and follicular infections.

Patient concerns: A 15-year-old boy had multiple rashes on the scalp accompanied by pain.

Diagnosis: The patient was diagnosed with PCAS or DCS based on the clinical manifestations and laboratory examinations.

Interventions: The patient was initially administered adalimumab 40mg biweekly and oral isotretinoin 30mg daily for 5months. Because the initial results were insufficient, the interval between adalimumab injections was extended to 4weeks, and isotretinoin was changed to baricitinib 4mg daily for 2months. When the condition became more stable, adalimumab 40mg and baricitinib 4mg were administered every 20 and 3days, respectively, for two more months until now.

Outcomes: After 9months of treatment and follow-up, the original skin lesions of the patient were almost cured, and most inflammatory alopecia patches disappeared.

Conclusion: Our literature review did not find any previous reports on treating PCAS with TNF-α inhibitors and baricitinib. Accordingly, we presented the first successful treatment of PCAS with this regimen.

KEYWORDS

PCAS, adalimumab, baricitinib, isotretinoin, case report

Introduction

Perifolliculitis capitis abscedens et suffodiens (PCAS) is a rare, refractory dermatitis that tends to recur frequently and primarily affects males with a dark phototype. The lesion, with an extensive infiltrate of neutrophils and lymphoid cells, develops into papules, pustules, and abscesses, which can further advance to the sinus and fistula. The resulting inflammation leads

to the formation of a granulation tissue called neutrophilic cicatricial alopecia. PCAS is a member of the "follicular occlusion tetrad," which also includes acne conglobate (AC), hidradenitis suppurativa (HS), and pilonidal sinus (1). The dominant pathogenic hypothesis involves follicular hyperkeratosis, which induces hair follicle obstruction, forcing the follicle to dilate and rupture, causing secondary infection and subsequent fistulas and abscesses (2). Although the etiology of PCAS is uncertain, several influencing factors, such as neutrophil infiltration, demographic parameter, hormonal risk factors, and the loss of immune tolerance to alloantigens in the hair follicle, may result in inflammation (3).

PCAS treatment is challenging. Isotretinoin and antibiotics are the general protocols for PCAS treatment; however, these drugs are not completely effective in this condition and easily cause relapse after their use is discontinued (3). Surgical excision and X-ray hair removal carry a higher risk of complications. Oral zinc and anti-androgens are utilized in mild to moderate cases (4). Recent case reports and clinical trials have mentioned tumor necrosis factor (TNF) inhibitors as viable PCAS treatments. To explore the potential of the anti-TNF antibody for treating PCAS, we presented the results of a case study and literature review related to an anti-TNF antibody administration to treat PCAS. However, a higher priority may be given to combination therapy because, when considering all of the available therapeutic options, a single treatment frequently has limited efficacy (5). The combined use of Janus kinase (JAK) inhibitors may potentially be a novel treatment scheme for PCAS.

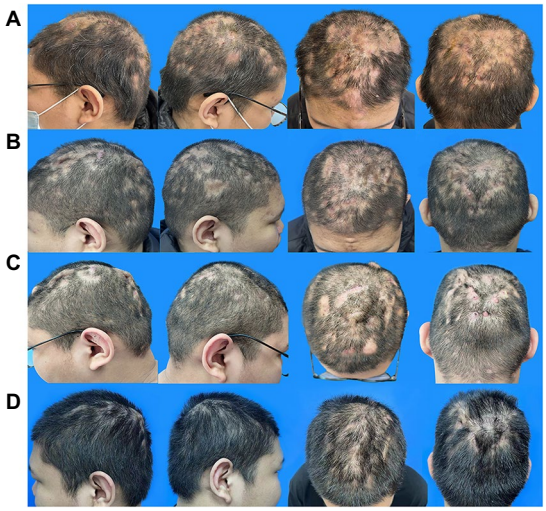

FIGURE 1
Evolution of the scalp manifestation of the PCAS patient. **(A)** Typical lesions of PCAS on the scalp, nodules, pustules, and alopecia patches prior to adalimumab and isotretinoin therapy on 17 February 2022. **(B)** After 1month of treatment with adalimumab and isotretinoin on 24 March 2022. **(C)** After 5months of treatment with adalimumab and isotretinoin on 23 July 2022. **(D)** After changing the treatment regimen to adalimumab and baricitinib for 4months on November 20, 2022. PCAS, Perifolliculitis capitis abscedens et suffodiens.

Case presentation

A 15-year-old Asian boy with a 10-month history of PCAS was referred to our hospital on 17 February 2022. The patient had multiple scalp rashes accompanied by itching, burning, and pain. Prior to hospital admission, the patient received antibiotic treatment with oral minocycline (50 mg twice daily) for 3 months and oral clindamycin (0.15 g four times daily) for 1 month. However, his clinical condition was not well controlled. The patient also consented to an operation to remove the abscess and drain the pus, which left five areas of scar hyperplasia but did not prevent relapses of the inflammatory lesions. The patient denied a history of smoking and family skin appendage disorders. The body mass index (BMI) of the patient was 26.2 (the normal BMI range for men is 18.5–23.9), which is a risk factor for PCAS (6).

Physical examination revealed several fluctuating pustules and prominent erythematous nodules on the scalp, the largest of which was located in the middle of the forehead (approximately 2 cm × 2 cm). The interconnecting sinuses of the patient were filled with malodorous pus, and extensive alopecia patches were located in the parietal-occipital scalp (Figure 1A).

Laboratory tests revealed a leukocyte, neutrophil, and lymphocyte count of 12.7×10^9/L, 9.1×10^9/L, and 19.8%, respectively, and a C-creative protein concentration of 3.38 mg/L. In addition, *Staphylococcus* was isolated from the pus of the lesion, and the drug susceptibility testing showed that Staphylococcus was sensitive to most antibiotics.

PCAS does not have a differential diagnosis or clear diagnostic criteria. Although pathological histological examination allows further observation, the histopathologic characteristics of PCAS usually depend on clinical manifestation. Therefore, the patient was diagnosed with PCAS or DCS according to the tendency, previous diagnosis, treatment history, clinical manifestations, and laboratory examinations of the patient.

Minocycline (50 mg twice daily) was used to control the inflammation from February 17. However, the lesions were not well controlled after 1 week as they were before. Therefore, after excluding contraindications, 80 mg adalimumab on day 0, followed by 40 mg every 2 weeks, and isotretinoin (30 mg daily) were adopted to alleviate the lesions. After 1 month, the patient scalp improved considerably, with fewer fresh pustules and less drainage. Furthermore, the alopecia patches were converted from an extensive wide range to scattered sections and the tenderness markedly subsided (Figure 1B). The laboratory tests revealed leukocyte, neutrophil, and lymphocyte counts of 5.0109/L, 2.5109/L, and 33.8%, respectively, and a C-creative protein concentration of 0.71 mg/L, indicating that the inflammatory response had been controlled.

After a 4-month follow-up, the level of triglycerides increased from 2.29 to 7.47 mmol/L, and the total cholesterol increased from 5.9 to 6.9 mmol/l compared to the values obtained upon patient admission to the hospital on February 18. These changes may be related to

Abbreviations: PCAS, Perifolliculitis capitis abscedens et suffodiens; DCS, Dissecting cellulitis of the scalp; AC, Acne conglobate; HS, Hidradenitis suppurativa; TNF, Tumor necrosis factor; TNFR1, Tumor necrosis factor receptor 1; TNFR2, Tumor necrosis factor receptor 2; JAK, Janus kinase; STAT, Signal transducers and activators of transcription; TYK2, Tyrosine kinase 2; FDA, US Food and Drug Administration.

isotretinoin and adalimumab administration. In addition, the skin lesions' improvement seemed to have plateaued (Figure 1C). As a result, fenofibrate (200 mg daily) was administered, and isotretinoin was discontinued to manage the above complications. The frequency of the adalimumab injections was also reduced to every 4 weeks, and baricitinib (4 mg daily) was creatively used as an anti-inflammatory agent and immunity regulator. After 1 month, the triglyceride level and total cholesterol decreased to 4.22 mmol/l and 6.1 mmol/L, respectively.

Following the second therapy round, the auriculotemporal lesions almost disappeared, and hair regrowth occurred naturally. However, some tiny pockets of pus persisted on the occiput. After 2 months, the prognosis appeared to have stabilized. Thus, the dosage of baricitinib was reduced to 4 mg every 3 days, and adalimumab injections were administered every 20 days. The lesions painlessly and infrequently leaked a tiny amount of pus after another 2 months of treatment, and most instances of alopecia recovered satisfactorily (Figure 1D). The laboratory tests revealed leukocyte, neutrophil, and lymphocyte counts of 6.9×10^9/L, 3.5×10^9/L, and 39.1%, respectively, and a C-creative protein concentration of 1.73 mg/L. Figure 2 shows the entire course of treatment.

We conducted a literature review in PubMed, Web of Science, Cochrane, and Scopus, valuing the role of TNF inhibitors treating PCAS on 25 February 2023. The database was searched using the terms "Perifolliculitis capitis abscedens et suffodiens" or "dissecting cellulitis" and "tumor necrosis factor" or" baricitinib." The search yielded 15 citations on 25 February 2023, comprising 19 patients with PCAS treated with TNF inhibitors after ineffective results with conventional treatments. The characteristics of the included studies are summarized in Table 1.

In the selected studies analyzed, all patients were males, with an average age of 32.47 ± 11.35 years (mean ± SD). The average duration of PCAS history was 8.1 ± 5.7 years (mean ± SD). The co-morbidity between PCAS and HS was 31.6%. Isotretinoin combined with antibiotics was the first-line treatment in 47.4% of PCAS cases. However, no obvious improvement was observed. Among the patients with PCAS administered TNF inhibitors, only one experienced no response, and two reported total clearance of the disease (7, 8). The remaining cases had marked pain reduction and inflammation relief. In particular, 89.5% of the patients with PCAS had pain relief, and 63.2% demonstrated complete cessation of pus. In addition, hair regrowth occurred in 63.2% of patients treated with TNF inhibitors.

On 25 February 2023, we also retrieved the English-language literature by searching the WHO trials register and Clinicaltrials.gov (clinical trial registries). Our search strategy focused on combination therapies providing a TNF inhibitor (adalimumab, infliximab, certolizumab pegol, etanercept, or golimumab) with a JAK inhibitor (baricitinib, tofacitinib, ruxolitinib, upadacitinib, or filgotinib). We found a single randomized controlled trial currently recruiting participants to study baricitinib in combination with adalimumab to treat RA (NCT04870203).

Discussion

PCAS is a well-known chronic and disfiguring disease. Current treatment for PCAS is non-standardized. In this case report, conventional integrated treatments with antibiotics, isotretinoin, and minor surgery failed to induce complete remission. The initial treatment regimen with isotretinoin and adalimumab led to the remnant of sinuses and areas of alopecia with hyperpigmentation, accompanied by elevated blood lipids. Eventually, we attempted an unprecedented approach and jointly administered adalimumab and baricitinib, which have never been explored as a combination regimen for treating PCAS.

A systematic literature review demonstrated that isotretinoin was administered to 53% of patients with PCAS, and a significant response was observed in half of those PCAS cases. However, the relapse rate was 19%. Antibiotics were administered to limit the disease in patients with milder PCAS conditions (4). Isotretinoin is assumed to normalize the skin and follicular apparatus to reduce the abnormal immune response. Antibiotics are effective supplements for moderating the inflammatory process, particularly during suspected secondary bacterial infection, like in our case. However, the unknown etiology, such as the inflammatory pathways in the skin of patients with PCAS, is responsible for the unsatisfactory recovery rate (9).

TNF-α is a cytokine involved in the pathogenesis of some inflammatory and autoimmune diseases. Therapeutic drugs act as antagonists by blocking the interaction of TNF-α with the type 1 (TNFR1) and type 2 (TNFR2) receptors. TNF-α inhibitors, including adalimumab, infliximab, golimumab, etanercept, and certolizumab, have been approved for clinical use (10). Among them, adalimumab and infliximab are frequently administered for treating PCAS. Adalimumab is a fully human monoclonal antibody, whereas infliximab is a recombinant chimeric monoclonal antibody (11). A retrospective evaluation revealed that the off-label use of TNF-α inhibitors to treat "follicular occlusion tetrads," which share the same pathogenesis with PCAS, had an extent impact on the outcome (7). Furthermore, adalimumab is a first-line biologic for patients with moderate-to-severe HS. TNF-α is the main driver of the inflammatory pathways predominant in HS skin lesions (12). From a clinical viewpoint, TNF-α inhibitors dramatically affected skin lesions and inflammatory symptoms in individual PCAS cases (13). Accordingly, adalimumab is speculated to be beneficial for treating PCAS. TNF-α inhibitors are novel biologics therapies and have garnered remarkable attention in recent years. However, these inhibitors have some limitations in scar restoration and hair regrowth (13). TNF-α inhibitors can minimize secretion, reduce inflammation, and relieve pain. Notably, the structural alteration of the tissue or promotion of blanket recovery by the TNF-α inhibitors is uncommon (14). Herein, we co-administered adalimumab and baricitinib to achieve a better outcome in a case of PCAS.

The JAK signal transducers and activators of transcription (STAT) are essential signaling pathways in various inflammatory diseases (15). JAK–STAT inhibition inhibits cytokine signaling to reduce the serum C-reactive protein levels. In mammals, there are four types of JAK family proteins: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Baricitinib is an oral selective and reversible inhibitor of JAK1 and JAK2 that inhibits JAK enzyme response to cytokine and the growth factor receptor stimulation to influence downstream hematopoiesis and immune cell function (16). Based on mounting clinical trials, JAK inhibitors have a promising prospect in dermatology and are effective for treating alopecia areata, atopic dermatitis, and psoriasis, as their relevant cytokines rely on the JAK–STAT pathway (17–20). In 2022, the safety and efficacy findings of two phase II studies demonstrated the positive role of the JAK1 inhibitor INCB054707 in HS patients

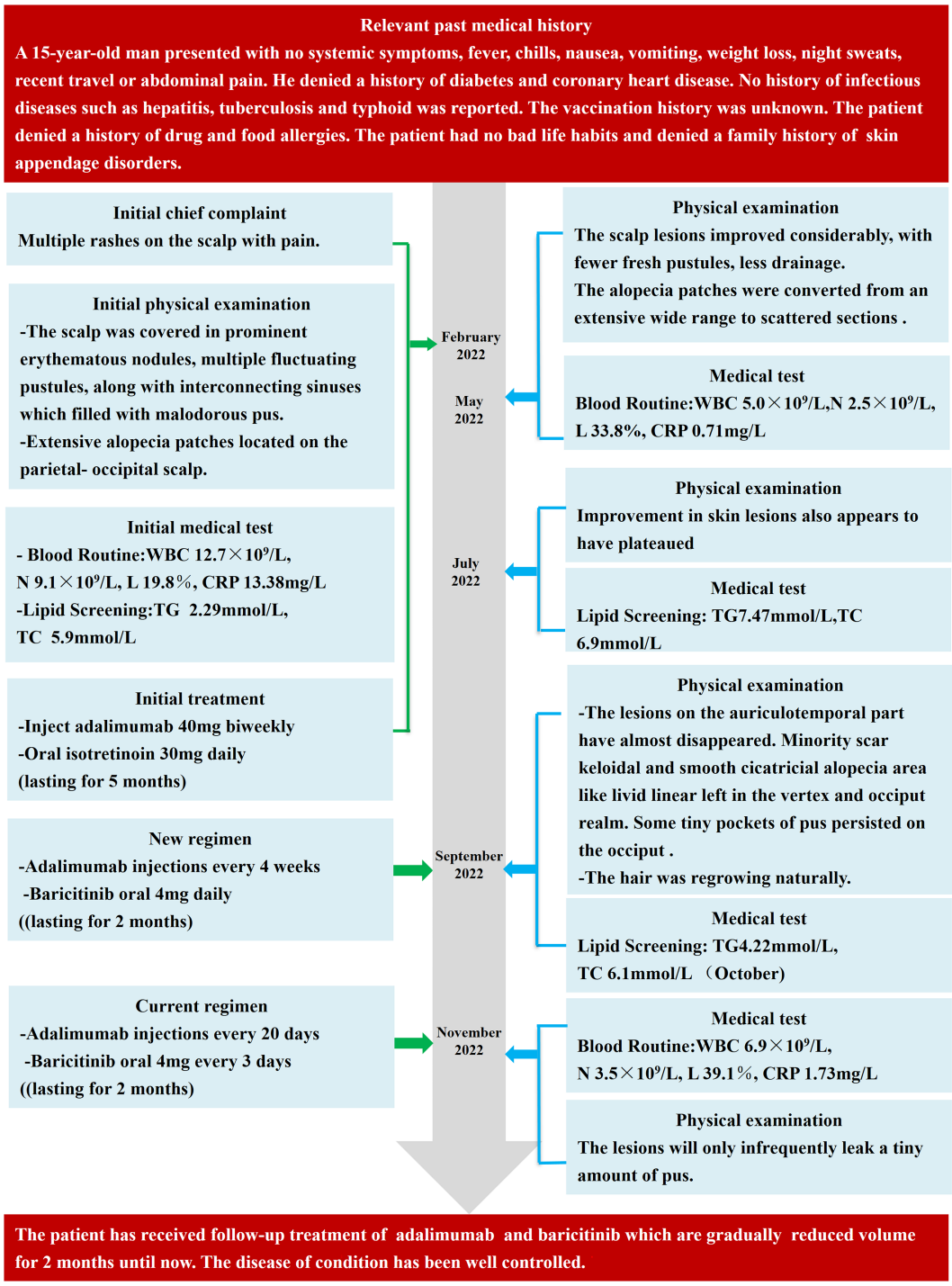

FIGURE 2
Important dates, periods, and detailed diagnostic process during the PCAS treatment and follow-up periods. WBC, white blood cells; N, neutrophils; L, Lymphocytes; ESR, erythrocyte sedimentation Rate; CRP, C-reactive protein; TG, triglyceride; TC, total cholesterol.

(21). Therefore, JAK1 may be a potential drug target in PCAS. In June 2022, the US Food and Drug Administration (FDA) approved baricitinib oral tablets to treat adult patients with severe alopecia areata, a disorder characterized by inflammatory, nonscarring patchy hair loss. As both alopecia areata and PCAS are types of inflammatory alopecia, baricitinib may have a similar therapeutic effect on PCAS. Baricitinib reduces inflammation in HS, and alopecia areata, and it displays potential as a drug for treating PCAS by dampening the inflammatory response. In our patient with PCAS, a significant reduction in scarring and visible hair regrowth at the site of the lesion were observed after the administration of baricitinib.

TNF-α and JAK inhibitors are used as biologics for treating psoriasis, inflammatory bowel disease, RA, and other diseases by inhibiting inflammatory signaling pathways. In some cases, the cascade response between the two inhibitors has been validated. Kandhaya-Pillai et al. demonstrated that JAK inhibitor interrupted

TABLE 1 Clinical characteristics of PCAS patients treated with tumor necrosis factor inhibitors.

No.	Authors	Demographic distribution (Age/Sex/Race)	Duration (Year)	Comorbidity	Previous treatments	TNF-alpha inhibitors	Outcomes (pain/ secretions/ hair regrowth)
1	Minakawa et al., 2021 (27)	30/M/Asian	12	HS	Oral antibiotics	Subcutaneous adalimumab	-/--/N.D.
2	Spiers et al., 2021 (28)	34/M/N.D.	N.D.	NCA, Ankylosing spondylitis	Oral antibiotics Oral isotretinoin	Subcutaneous 40 mg adalimumab fortnightly Serial scalp excisions	-/--/-
3	Alsantali et al., 2021 (29)	38/M/N.D.	5	NONE	Oral antibiotics Oral isotretinoin	Adalimumab*	-/--/N.D.
4	Kurokawa et al., 2021 (30)	18/M/Asian	6	HS, NCA	Oral antibiotics	Subcutaneous 160 mg adalimumab on day 0, and 80 mg every other week	-/N.D./-
5	Maxon et al., 2020 (31)	37/M/AA	13	Cystic acne	Oral isotretinoin Corticosteroid injections	Subcutaneous 40 mg adalimumab once weekly	-/N.D./-
6	Takahashi et al., 2019 (13)	19/M/Asian	5	HS	Oral antibiotics Zinc supplementation	Adalimumab*	-/--/-
7	Masnec et al., 2018 (32)	26/M/N.D.	N.D.	HS NCA	Oral antibiotics Oral isotretinoin	Subcutaneous 80 mg adalimumab on days 0,1, and 14 followed by 40 mg on day 28 and every week thereafter	-/-/N.D.
8	Mansouri et al., 2016 (33)	48/M/Afro-Caribbean	20	HS	Oral antibiotics Oral isotretinoin Systemic corticosteroids Zinc sulfate Minor surgery	Adalimumab*	-/--/N.D.
9	Mansouri et al., 2016 (33)	27/M/Caucasian	4	NONE	Oral antibiotics Oral isotretinoin Topical and systemic corticosteroids	Infliximab*	-/--/N.D.
10	Martin-García and Rullán, 2015 (34)	30/M/Caucasian	15	NONE	Oral antibiotics. Oral isotretinoin. Minor surgery	Adalimumab*	--/--/-
11	Freja Lærke Sand et al., 2015 (7)	N.D./M/D.M.	N.D.	N.D.	Dapsone Oral isotretinoin Triamcinolone	Subcutaneous adalimumab 40 mg once weekly	Total clearance of the disease

(Continued)

TABLE 1 (Continued)

No.	Authors	Demographic distribution (Age/Sex/Race)	Duration (Year)	Comorbidity	Previous treatments	TNF-alpha inhibitors	Outcomes (pain/ secretions/ hair regrowth)
12	Freja Lærke Sand et al., 2015 (7)	N.D./M/D.M.	N.D.	N.D.	Oral antibiotics. Oral isotretinoin Corticosteroid	Subcutaneous adalimumab 40 mg once weekly	Did not respond
13	Lim et al., 2013 (8)	66/M/AA	14	Acne vulgaris. Sycosis barbae	Oral antibiotics. Topical corticosteroids. Rifampin	Subcutaneous adalimumab 40 mg once weekly and oral antibiotics	Total clearance of the disease
14	Navarini et al., 2012 (35)	30/M/N.D.	1	AC, Type2 diabetes mellitus	Oral isotretinoin Corticosteroids. Minor surgery. Rifampicin	Infliximab* (intravenous)	-/--/N.D. Developed a temporary psoriasiform rash after the second intravenous infusion
15	Navarini et al., 2010 (14)	30/M/Caucasian	1	NONE	Oral antibiotics	Adalimumab*	-/-/-. Preexisting pathologic residual structures remained unchanged
16	Navarini et al., 2010 (14)	29/M/Caucasian	4	NONE	Oral antibiotics. Oral isotretinoin	Adalimumab*	-/--/-. Preexisting pathologic residual structures remained unchanged
17	Navarini et al., 2010 (14)	27/M/Caucasian	7	HS	Oral antibiotics. Oral isotretinoin	Adalimumab*	-/N.D./- Preexisting pathologic residual structures remained unchanged. When adalimumab administration was paused, relapse occurred within 4 weeks
18	Brandt et al., 2008 (36)	24/M/N.D.	N.D.	NONE	NA	Infliximab 5 mg·kg^{-1} infused at 8-week intervals	N.D./N.D./-
19	Sukhatme et al., 2008 (37)	39/M/ Caucasian	6	NONE	Minor surgery. Oral isotretinoin	Adalimumab*	--/--/-

N.D.: not described; AA: African-American; NCA: nodulocystic acne; AC: acne conglobata; HS: hidradenitis suppurativa; Adalimumab*: 80 mg Adalimumab was administered on day 0, followed by 40 mg weekly (treated according to the recommended psoriasis regimen); Infliximab*: 5 mg kg^{-1} infliximab was administered in weeks 0, 2, and 6, followed by 8-week intervals (treated according to the recommended psoriasis regimen); -: relieve, --: Cease.

the interactive loop between the synergy of TNF-α and IFN-γ to prevent hyper-inflammation and normalize SARS-CoV-2 entry receptor expression (22). In addition, a study showed that TNF-α was significantly reduced in adult patients with systemic lupus erythematosus treated with baricitinib (23). By pathway analysis, Krisztina et al. have revealed the involvement of TNF and JAK–STAT signaling in the complex regional pain syndrome, which presents severe chronic pain, hypersensitivity, and inflammation. Baricitinib can also compensate for inadequate response to tumor necrosis factor inhibitors (TNFis). In a retrospective therapeutic drug monitoring case series, patients with HS, with anti-adalimumab antibody, had significantly lower serum adalimumab levels. In addition, the patients with HS in the supratherapeutic groups were treated for a significantly longer time period than the therapeutic patients (24). Baricitinib has also been reported to outperform TNFis in the treatment of RA (25).

In summary, we administered baricitinib to patients with PCAS to interrupt TNF-α and IFN-γ inflammatory pathways and help them

compensate for their suboptimal response to adalimumab treatment. Our results showed that this combinatorial treatment was indeed beneficial. Given the potential for increased frequency of serious adverse events (including heart disease, blood clots, infections, and anemia) when combining targeted therapies, we are very cautious in setting the dosage of the two medications. According to a meta-analysis published in 2022, JAK inhibitor was discontinued more often among patients with RA for adverse events, and less often for inefficacy compared to TNF inhibitor (26). Treatment continues to be dominated by adalimumab, with baricitinib playing an adjuvant role. Although combining the two drugs increases the risk of an adverse event, it remains worth trying within a manageable range for refractory conditions in which patients have experienced multiple treatment failures. Baricitinib alone may also be a viable option, but we are testing it under the premise that adalimumab is effective against HS, and adalimumab did provide relief in this case. We thus opted to continue with combination therapy for our second round of treatment.

A combination of treatment modalities is often necessary to optimize treatment outcomes. We provide a feasible solution for patients who do not fully respond to TNF-α inhibitors, or who have tenacious scarring and hair loss sequelae. However, the role of TNF-α and JAKs in the pathogenesis of PCAS has not been established. Our experience of treating PCAS is based on the HS and AA populations. Considering the relative lack of studies on the immunology of this condition, a fundamental understanding of immunological dysregulation in PCAS is urgently required. In the future, more standard evaluation criteria, and robust studies, including randomized control trials, are required to determine the preferred treatment options.

Author's note

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

YY conducted the literature search and drafted the manuscript. XD was responsible for the clinical treatment of the patient, meanwhile she revised and polished the thesis in post. FG were involved in patient management and contributed to metadata acquisition and interpretation. KZ, XS, and XL critically reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by The National Natural Science Foundation of China (No. 82074427), the Clinical Research Plan of SHDC (No. SHDC2020CR3097B), the Shanghai Sailing Program (No. 20YF1450400), Shanghai Three-Year Action Plan to Further Accelerate the Inheritance and Innovative Development of Chinese Medicine (2021–2023) [No. ZY(2021–2023)-0302], and the Three-Year Action Plan for Further Accelerating the Inheritance and Innovative Development of Chinese Medicine in Shanghai (2021–2023) [No. ZY(2021–2023)-0209-13].

Acknowledgments

We thank the patient and his family for participating in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 30 May 2023
DOI 10.3389/fmed.2023.1093827

OPEN ACCESS

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RECEIVED 09 November 2022
ACCEPTED 02 May 2023
PUBLISHED 30 May 2023

CITATION
Minakawa S, Matsuzaki Y, Yao S, Sagara C, Akasaka E, Koga H, Ishii N, Hashimoto T and Sawamura D (2023) Case report: A case of epidermolysis bullosa acquisita with IgG and IgM anti-basement membrane zone antibodies relapsed after COVID-19 mRNA vaccination. *Front. Med.* 10:1093827.
doi: 10.3389/fmed.2023.1093827

Case report: A case of epidermolysis bullosa acquisita with IgG and IgM anti-basement membrane zone antibodies relapsed after COVID-19 mRNA vaccination

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We report a case of autoimmune bullous disease (AIBD) with IgG and IgM autoantibodies against epidermal basement membrane zone (BMZ), which showed recurrence of mucocutaneous lesions after coronavirus disease 2019 (COVID-19) mRNA vaccination. A 20-year-old Japanese woman with a 4-year history of epidermolysis bullosa acquisita (EBA) presented to our clinic. She noticed fever and rash on the same day and visited at our hospital 2 days later. Physical examination revealed blisters, erosions and erythema on the face, shoulder, back, upper arms, and lower lip. A skin biopsy from the forehead showed subepidermal blister. Direct immunofluorescence showed linear depositions of IgG, IgM, and C3c in the epidermal BMZ. By indirect immunofluorescence of 1M NaCl-split normal human skin, circulating IgG autoantibodies were bound to the dermal side of the split at 1:40 serum dilution, and circulating IgM antibodies were bound to the epidermal side of the spilt. After the increase of prednisolone dose to 15 mg/day, the mucocutaneous lesions resolved in a week. The present case is the first case of possible EBA with IgG and IgM anti-BMZ antibodies, in which the mucocutaneous lesions were recurred after COVID-19 mRNA vaccination. Clinicians should be aware that bullous pemphigoid-like AIBDs, including EBA and IgM pemphigoid, might be developed after COVID-19 mRNA vaccination.

KEYWORDS

autoimmune blistering diseases, EBA, immunofluorescence, enzyme-linked immunosorbent assay (ELISA), type VII collagen

Introduction

Autoimmune bullous diseases (AIBDs), a group of tissue specific autoimmune disease of the skin, are classified into various subtypes with the different immunoglobulin types and autoantigens (1). Epidermolysis bullosa acquisita (EBA) is characterized clinically by blisters and scars of the skin and erosive mucosal lesions, and immunologically by IgG autoantibodies against type VII collaegen (2, 3). In many EBA cases, oral administration of corticosteroids are effective but do not lead to complete remission.

AIBDs have been reported to be induced or exacerbated after immunization with various vaccines, including vaccines for measles, varicella zoster, influenza, hepatitis B and human papillomavirus (4).

The rapid flare of a bullous diseases after vaccination is not novel. Bullous pemphigoid (BP) has been reported to occur within 24 hours after vaccination (5). In addition, among the 12 patients who newly developed subepidermal blistering lesions after the first or second coronavirus disease 2019 (COVID-19) mRNA vaccination, the diagnosis of BP was confirmed in eight patients by the results of direct immunofluorescence (DIF), indirect immunofluorescence (IIF) of 1 M NaCl-split skin and/or enzyme-linked immunosorbent assays (ELISA) of BP180 (6).

In this report, we present with a case of EBA with IgG and IgM autoantibodies against epidermal basement membrane zone (BMZ), which showed recurrence of mucocutaneous lesions 2 days after COVID-19 mRNA vaccination.

Case report

A 16-year-old Japanese female presented with a 1-month history of erosions on the lips. She had no medical history. Physical examination revealed blisters, erosions and erythema on the face (Figure 1a), lips, back, shoulders (Figure 1b) and arms (Figure 1c). Histopathology for a skin biopsy from the face showed subepidermal blisters. DIF showed linear depositions of IgG, IgM, and C3c in the epidermal BMZ (data not shown).

Circulating IgG anti-BMZ autoantibodies were detected by IIF of normal human skin, which bound to the dermal side of 1 M NaCl-split normal human skin at 1:40 serum dilution (Figure 2a). Circulating IgM autoantibodies were bound to the epidermal side of 1 M NaCl-split normal human skin at 1:40 serum dilution (Figure 2b). IgG ELISAs (MBL, Japan) showed positive results for type VII collagen (index 39.76; cut-off <6.14), but negative for desmoglein 1, desmoglein 3, BP180 and BP230. Immunoblotting of normal human dermal extract detected IgG antibodies to type VII collagen (Figure 2c), while IgG immunoblotting analyses of other substrates were negative. IgM immunoblotting analyses of normal human epidermal extracts, recombinant proteins of NC16a and C-terminal domains of BP180 and concentrated culture supernatant of HaCaT cells were negative.

The diagnosis of EBA with IgM antibodies to unknown antigen was made, and the initiation of oral prednisolone 30 mg/day gradually improved the skin and oral mucosal symptoms. However, the skin lesions were intaractable, and the patient stayed on prednisolone for the 4 years until the recurrence, when the patient was treated with prednisolone 2 mg/day.

Four years later, after the patient received first dose of COVID-19 mRNA vaccination, she first noticed fever on day 1 on the same day and then bullous skin lesions 2 days later. Then the patient visited at our hospital. Physical examination revealed blisters, erosions and erythema on the face (Figure 1d), shoulder, back, upper arms, and lower lip (Figure 1e). A skin biopsy from the forehead histopathologically showed subepidermal blisters (Figures 1f, g). DIF showed linear depositions of IgG, IgM, and C3c, but not IgA, in the epidermal BMZ (Figures 2d–g).

By IIF of 1M NaCl-split normal human skin, circulating IgG autoantibodies were bound to the dermal side of the split at 1:40 serum dilution (Figure 2h), and circulating IgM antibodies were bound to the epidermal side of the spilt (Figure 2i). IgG type VII collagen ELISA was negative (index 5.78; cut-off < 6.14). Immunoblotting of normal human dermal extract did not detect IgG antibodies to type VII collagen (Figure 2c). IgM immunoblotting analyses using the 4 substrates were negative. The results of various immunological tests both at the first visit 4 years before and after the COVID-19 mRNA vaccination were summarized in Table 1.

After the increase of prednisolone dose form 2 to 15 mg/day, the mucocutaneous lesions resolved in a week.

Discussion

COVID-19 mRNA vaccination has been reported to induce not only AIBDs but also many other skin conditions (7). From the positive results in DIF and IIF analyses, as well as the clinical features of prominent blisters, we considered that the present case might have had a relapse of EBA by COVID-19 mRNA vaccination 4 years after the first visit, although the 2 days may not be too short for the recurrence of autoimmune disease, and we could not detect specific autoantigens at this recurrent time.

Regarding the precise diagnosis for the present case, at the first visit, the results of various immunological tests, including positive IgG reactivity with type VII collagen, made the diagnosis of EBA, although IgM anti-BMZ antibodies co-existed.

The mucocutaneous lesions recurred after COVID-19 mRNA vaccination were most likely the recurrence of EBA from the positive IgG reactivity with dermal side of 1 M NaCl-split skin, although we could not detect IgG reactivity with type VII collagen. The reason for the failure to detect anti-type VII collagen might be either that the antibody titer was too low or that the epitope on type VII collagen had changed. The possibility of the change from EBA to the other AIBDs with IgG reactivity with dermal side, i.e., anti-laminin 332-type mucous membrane pemphigoid (MMP) or ant-p200 pemphigoid, is less conceivable.

Recently, Hirano et al. (8) proposed IgM pemphigoid, which showed anti-epidermal BMZ antibodies exclusive of IgM type, as a novel AIBDs entity. However, the disease entity of IgM pemphigoid has not been widely accepted. The clinical and histopathological characteristics, as well as the therapies and disease course, in IgM pemphigoid remain unknown. IgM autoantibodies in IgM pemphigoid tend to react with non-NC16A domain of BP180, probably C-terminal domain (8). Another possibility is that this case had IgM pemphigoid, and IgM anti-BMZ antibodies caused the mucocutaneous lesions both at the onset and at the time of relapse.

An older study suggested that IgM deposits (granular and linear) are present in the sun-exposed skin of healthy adults (*n*

Abbreviations: AIBDs, autoimmune bullous diseases; BMZ, basement membrane zone; BP, bullous pemphigoid; COVID-19, coronavirus disease 2019; DIF, direct immunofluorescence; EBA, epidermolysis bullosa acquisita; ELISA, enzyme-linked immunosorbent assays; IIF, indirect immunofluorescence; MMP, mucous membrane pemphigoid; ss-IIF, salt split skin indirect immunofluorescence.

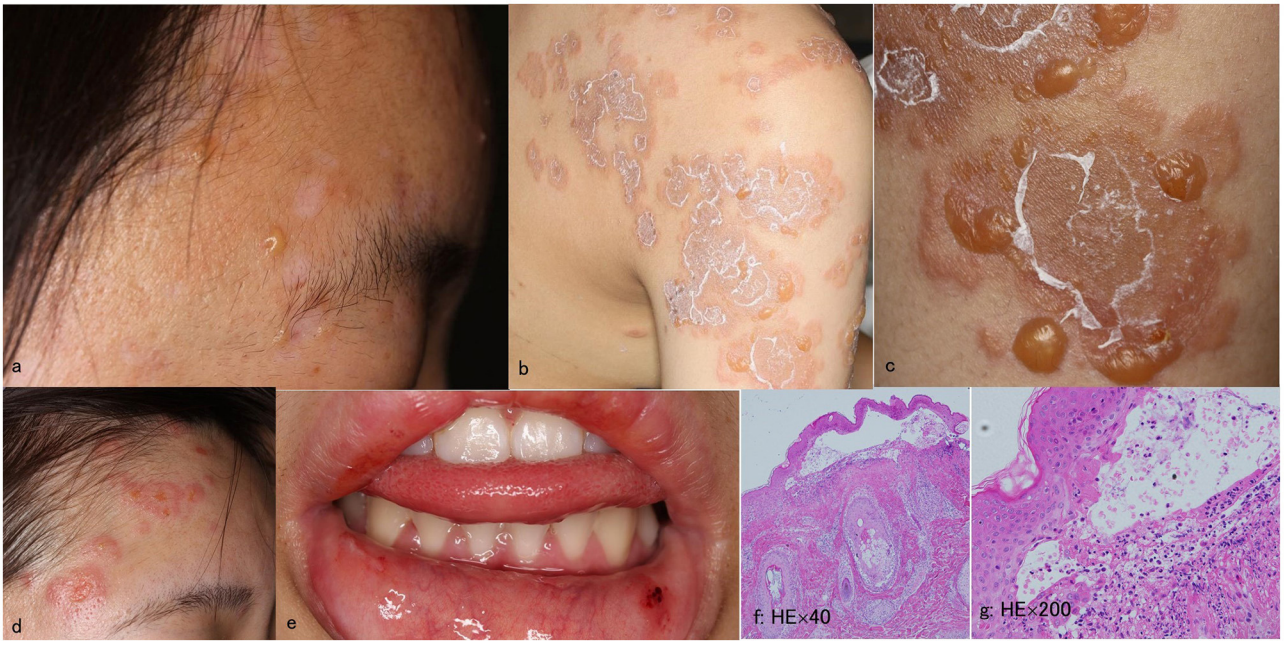

FIGURE 1
Clinical and histopathological features at the first visit and at the time of relapse. **(a–e)** Clinical features of blisters, erosions, and erythema on the forehead **(a)**, shoulder **(b)**, and upper arms **(c)** at the first visit, and those on the face **(d)**, and lower lip **(e)** at the time of relapse. **(f, g)** Histopathology of the skin biopsy from the forehead at the time of relapse showing subepidermal blisters with infiltration of neutrophils in the blister and dermis [original magnifications; **(f)** ×40 and **(g)** ×200].

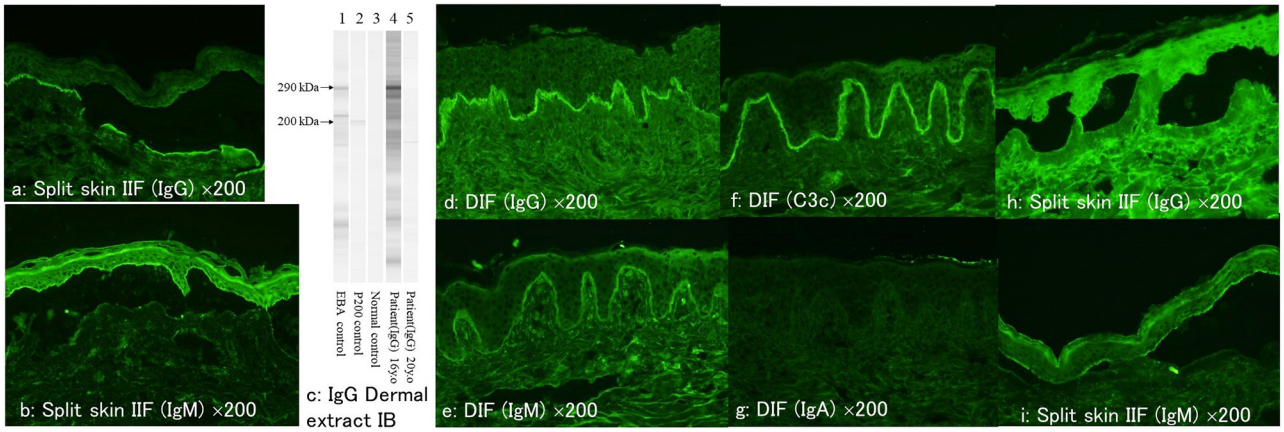

FIGURE 2
The result of various immunological tests at the first visit and at the time of relapse. **(a, b)** At the first visit, indirect immunofluorescence of 1M NaCl-split skin showing positive reactivity with dermal side for IgG antibodies **(a)** and with epidermal side for IgM antibodies **(b)**. **(c)** The results of IgG immunoblotting of normal human dermal extract. The serum at the first visit (lane 4), but not the serum at the relapse (lane 5), reacted with the 290 kDa type VII collagen. **(d–g)** Direct immunofluorescence at the time of relapse showing positive results for IgG **(d)**, IgM **(e)**, and C3c **(f)** but negative for IgA **(g)**. **(h, i)** At the time of relapse, indirect immunofluorescence of 1 M NaCl-split skin showing positive reactivity with dermal side for IgG antibodies **(h)** and with epidermal side for IgM antibodies **(i)** (all of the immunofluorescence figures: original magnification, ×200).

= 10/41) (9). Other studies also identified linear IgM deposits in various bullous and non-bullous skin disorders (9). Although the true pathogenic role of the IgM antibodies is unknown, the fact that IgM antibodies were present at both the initial and recurrence stages, while IgG anti-type VII collagen antibodies were not detected at the recurrence stage might suggest the pathogenic relevance of the IgM antibodies.

Previous studies reported that various autoimmune skin diseases, including AIBDs, developed skin lesions about 1 week after COVID-19 vaccination with some variation (10, 11). This case showed the recurrence only 2 days after vaccination, and therefore it may be difficult to conclude that the recurrence of the skin lesions is attributed to vaccination. Indeed, 2 days are too short for pathogenic plasma cells to produce autoantibodies.

TABLE 1 The summary of the results of various immunological tests both at the first visit 4 years before and at the time of relapse after the COVID-19 vaccination.

	First visit (16 year old)	Relapse (20 year old)
DIF (BMZ) IgG	(+)	(+)
DIF (BMZ) IgA	(–)	(–)
DIF (BMZ) IgM	(+)	(+)
DIF (BMZ) C3c	(+)	(+)
IIF (BMZ) IgG	(+) × 40	(–)
IIF (BMZ) IgM	(–)	(–)
ss-IIF (epidermis) IgG	(–)	(–)
ss-IIF (epidermis) IgM	(+) × 10	(+) × 40
ss-IIF (dermis) IgG	(+) × 40	(+) × 40
ss-IIF (dermis) IgM	(–)	(–)
IgG Dermal extract IB: 290 kDa	Pos	Neg
IgG Dermal extract IB: 200 kDa	Neg	Neg
IgG Dermal extract IB: laminin 332	Neg	Neg
IgG ELISAs type VII collagen (cut-off Index <6.14)	39.76	5.78
Anti-BP180 NC16A IgG ELISA	Neg	Neg
Anti-BP230 IgG ELISA	Neg	Neg

BMZ, basement membrane zone; DIF, direct immunofluorescence; IB, immunoblotting; IIF, indirect immunofluorescence; Neg, negative; Pos; positive; ss-IIF, 1M NaCl split skin indirect immunofluorescence; (+), linear deposits of immunoreactants; (–), no deposits of immunoreactants.

However, there may be different mechanisms for the quick recurrence of the skin lesions. For example, the autoantibodies were persisted in the serum in this patient, and some triggers caused by vaccination might reactivate the pathogenic activity of the autoantibodies. One possibility might be similar to the mechanism in vancomycin-induced linear IgA disease, in which recurrence of the skin lesions occurred after few days of vancomycin intake, through the activation of preexisting IgA anti-collagen VII antibodies by binding of vancomycin to IgA antibodies (12).

In addition, a previous report described that the relapses of some skin diseases were seen very early (even on day 2) after COVID-19 vaccination. Therefore, we considered that this case might recur the previous autoimmune skin disease after vaccination (13).

Characteristic clinical features in our patient were prominent vesicular erythematous skin lesions on the face and severe oral mucosal lesions. Skin lesions on the face are rarely seen in both common BP and EBA (2, 3, 14–17). In addition, oral mucosal lesions are frequently seen in EBA, but are uncommon in BP (16, 17). Therefore, the prominent facial skin lesions and severe oral mucosal lesions in our patient might be cause by COVID-19 vaccination or IgM anti-BMZ autoantibodies.

EBA is a heterogeneous disease (18). In our case, the lesions are present on the mucosa and the face which is not common in normal BP. The cutaneous manifestations in EBA can be classified into two major clinical subtypes: non-inflammantory (classical or mechanobullous) and inflammatory EBA, which is characterized by cutaneous inflammation, resembling BP, linear IgA disease, MMP, or Brunsting-Perry pemphigoid (15).

The facial involvement is not uncommon, especially in the Brunsting-Perry pemphigoid-like variant of EBA, which is confined to the head and neck, was originally described in 1957 in seven patients with localized cicatricial pemphigoid (19). Similar findings have also been reported in patients with BP and EBA (20, 21). All these disorders have a common subepidermal clefting or blistering and linear IgG/complement deposition by DIF with autoantibodies against variable BMZ components such as BP180, BP230, laminin-332, and collagen VII (22).

The cutaneous manifestations of an individual EBA patients may change during the course of disease, or the same patients may present with two different forms simultaneously (14). Many EBA patients have not to lead to complete remission by the treatment (23). If disease activity cannot be controlled. Oral lesions are most commonly observed in patients with non-inflammatory EBA and those with MMP-like or LAD-like inflammatory EBA. Hence, we diagnosed her as the recurrence of non-inflammatory EBA.

In viral infections, IgM develops early stage. IgM levels increased during the first week after SARS-CoV-2 infection, peaked 2 weeks and then reduced to near-background levels in most patients (24). IgG was detectable after 1 week and was maintained at a high level for a long period (24).

In conclusion, the present case is the first case of possible EBA with IgG and IgM anti-BMZ antibodies, in which the mucocutaneous lesions were recurred 2 days after COVID-19 mRNA vaccination. Clinicians should be aware that BP-like AIBDs, including EBA and IgM pemphigoid, might be developed after COVID-19 mRNA vaccination. However, because corticosteroid treatment might have a beneficial effect on COVID-19, abrupt termination or quick dose reduction of systemic corticosteroids should be avoided in severe AIBDs (25).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The Committee of Medical Ethics of Hirosaki University Graduate School of Medicine approved the research study. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

TH and SM contributed to conception and organized the data. SY and CS contributed to collect samples. NI and HK performed

the statistical analysis. SM wrote the first draft of the manuscript. TH, YM, and EA editing the manuscript. DS decided to submit report for publication. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported in part by A Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (project 20k08684 to SM) and by the 2022 Hirosaki University Research Support System.

Acknowledgments

We are grateful to the patient for providing written informed consent to publication. We express our gratitude to Mrs. Mayumi Tamada and Mrs. Kyoko Hiromatsu, Department of Dermatology, Kurume University School of Medicine, Fukuoka, Japan for immunoblotting analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 14 August 2023
DOI 10.3389/fmed.2023.1125754

OPEN ACCESS

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RECEIVED 16 December 2022
ACCEPTED 13 July 2023
PUBLISHED 14 August 2023

CITATION
Paulmann M, Reinkemeier F, Lehnhardt M and Mockenhaupt M (2023) Case report: Generalized bullous fixed drug eruption mimicking epidermal necrolysis.
Front. Med. 10:1125754.
doi: 10.3389/fmed.2023.1125754

Case report: Generalized bullous fixed drug eruption mimicking epidermal necrolysis

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Generalized bullous fixed drug eruption (GBFDE) is the most severe form of fixed drug eruption and can be misdiagnosed as epidermal necrolysis (EN). We report the case of a 42-year-old male patient presenting with more than 50% skin detachment without defined areas of exanthema or erythema and a history of one prior event of EN caused by acetaminophen (paracetamol), allopurinol, or amoxicillin 1.5 years ago. The initial diagnosis was GBFDE or EN. The histology of a skin biopsy was unable to distinguish between the two diseases. The course of the disease, the later clinical presentation, and the medical and medication history, however, were in favor of a diagnosis of GBFDE with two potentially culprit drugs: metamizole and ibuprofen. Moxifloxacin, enoxaparin sodium, hydromorphone, and insulin human were administered concomitantly, which makes them suspicious as well. Unfortunately, the patient received an additional dose of metamizole, one of the possible causative drugs, and he developed another bullous reaction within 1 month. This led to the diagnosis of GBFDE due to metamizole. This report highlights the challenges of distinguishing two rare diseases and elucidates the importance of distinct clinical presentation and detailed medication history.

KEYWORDS

case report, generalized bullous fixed drug eruption, epidermal necrolysis, recurrence, re-exposure, metamizole, GBFDE

1. Introduction

Fixed drug eruption (FDE) is an adverse reaction to multiple drugs and sometimes food (1). FDE is characterized by a limited number of well-demarcated solitary erythematous or violaceous patches of round to oval shape leaving hyperpigmentation after healing. Additionally, blisters or erosions can occur on these patches (2–5). An erosive involvement of oral and/or genital mucous membranes is rarely present and if present, then rather mild (3, 4, 6). Re-exposure to the causative drug leads to a same-site recurrence of these patches, whereas the lesions can increase in size and number (1, 5, 7, 8). In rare cases, the patches occur in generalized distribution with extensive detachment. This type of FDE is called generalized bullous fixed drug eruption (GBFDE) (2, 6). In addition to the variant of clearly demarcated patches, there is a variant of GBFDE with diffuse generalized erythema subsequently showing flaccid blisters (4, 9). Both types of GBFDE can resemble the presentation of epidermal necrolysis (EN), and that is why GBFDE is often misdiagnosed as EN (1, 2, 6, 10). EN is a term, which describes a disease spectrum that includes Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and their overlap (11–14). SJS and TEN represent a continuum of a rare, severe cutaneous adverse reaction, which

is characterized by spots and atypical targets with skin detachment and erosive mucous membranes (6, 13, 15). The epidermal detachment in cases of SJS is <10% of the body surface area (BSA), in TEN, more than 30% BSA, and in SJS/TEN overlap, 10–30% BSA (15).

We present a case with two events of extensive skin detachment within 1 month and a final diagnosis of GBFDE after the second event.

2. Case description

A 42-year-old Thai man with a history of polytoxicomania (abuse of alcohol, drugs, and nicotine), arterial hypertension, diabetes mellitus type II, hepatic steatosis, depression, and EN presented to the emergency department due to a fall 1 day before. The head injury required several stitches, and the patient was discharged. In the evening, he experienced deterioration of his general state of health, nausea, emesis, fever, impaired vision, and swelling of his face. Due to further aggravation of these symptoms, the patient presented to the local hospital, where he was admitted to the internal medicine department with hypotension, tachycardia, hypoxia, and increased laboratory values for kidney parameters and C-reactive protein (CRP). Antibiotic treatment with moxifloxacin was initiated, and 100 mg prednisolone i.v. was given. Two days later, he developed a mild exanthema/erythema with skin blisters on the back and limbs as well as a positive Nikolsky I sign, but without mucosal erosions. The consultant dermatologist made a diagnosis of recurrent EN of unknown origin due to taking multiple medications (Figure 1) and took a biopsy. The patient had been treated at this hospital 1 year before because of the acute onset of a severe skin reaction with generalized blisters on the face, back, palms, and soles. In addition, there had been erosions of lips and oral mucosa. The diagnosis by the consultant dermatologist then was EN related to the intake of acetaminophen (paracetamol). allopurinol and amoxicillin were also suspected.

The patient reported that he had not taken acetaminophen (paracetamol) this time but other pain medications (Figure 1). However, there were contradictory statements from the patient and his caretaker regarding 6 July 2017. The patient denied taking metamizole that day, while the caretaker confirmed that he had taken it. The opposite was reported for taking ibuprofen. Nonetheless, both substances were started just before the onset of the reaction (9th July 2017), whereas this short exposure period is only appropriate for GBFDE not for EN. Moxifloxacin, enoxaparin sodium, hydromorphone, and insulin human were also administered during the same period, making them suspicious as well. Considering the relevant period of 4–28 days of drug use to induce EN, no causative drug could be identified. Overall, the drug history should be evaluated with caution due to the polytoxicomania (especially alcohol abuse) of the patient. To determine the cause of the reaction, it was suggested to perform a patch test *in loco* within 2–6 months after discharge.

The skin biopsy showed a subepidermal blister and detached epidermis with florid interface dermatitis and many necrotic keratinocytes as well as mild interstitial and perivascular superficial

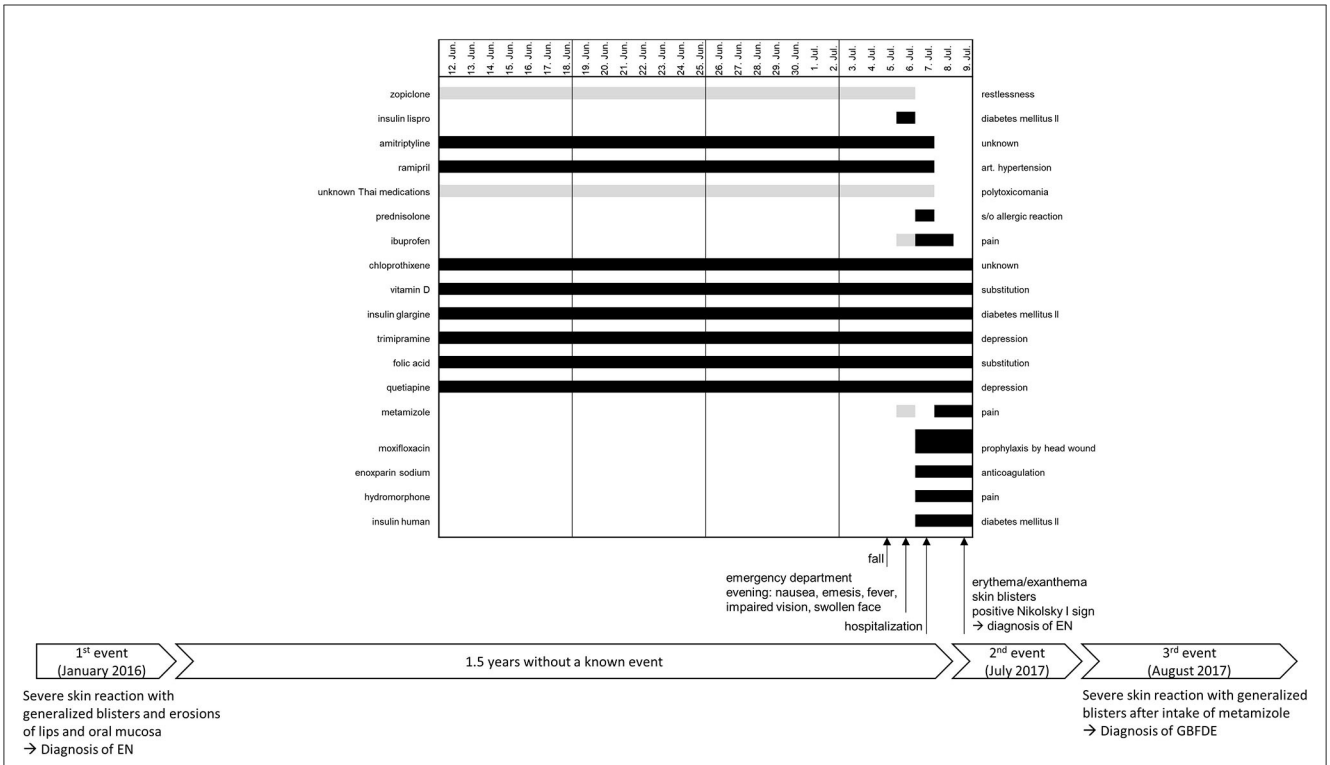

FIGURE 1
Timeline of the three known events with a detailed medication history of the last 4 weeks before the onset of the severe skin reaction on 9 July 2017. The black bars represent the daily intake of a drug, and the gray bars represent an intermittent or unknown intake. GBFDE, generalized bullous fixed drug eruption; EN, epidermal necrolysis.

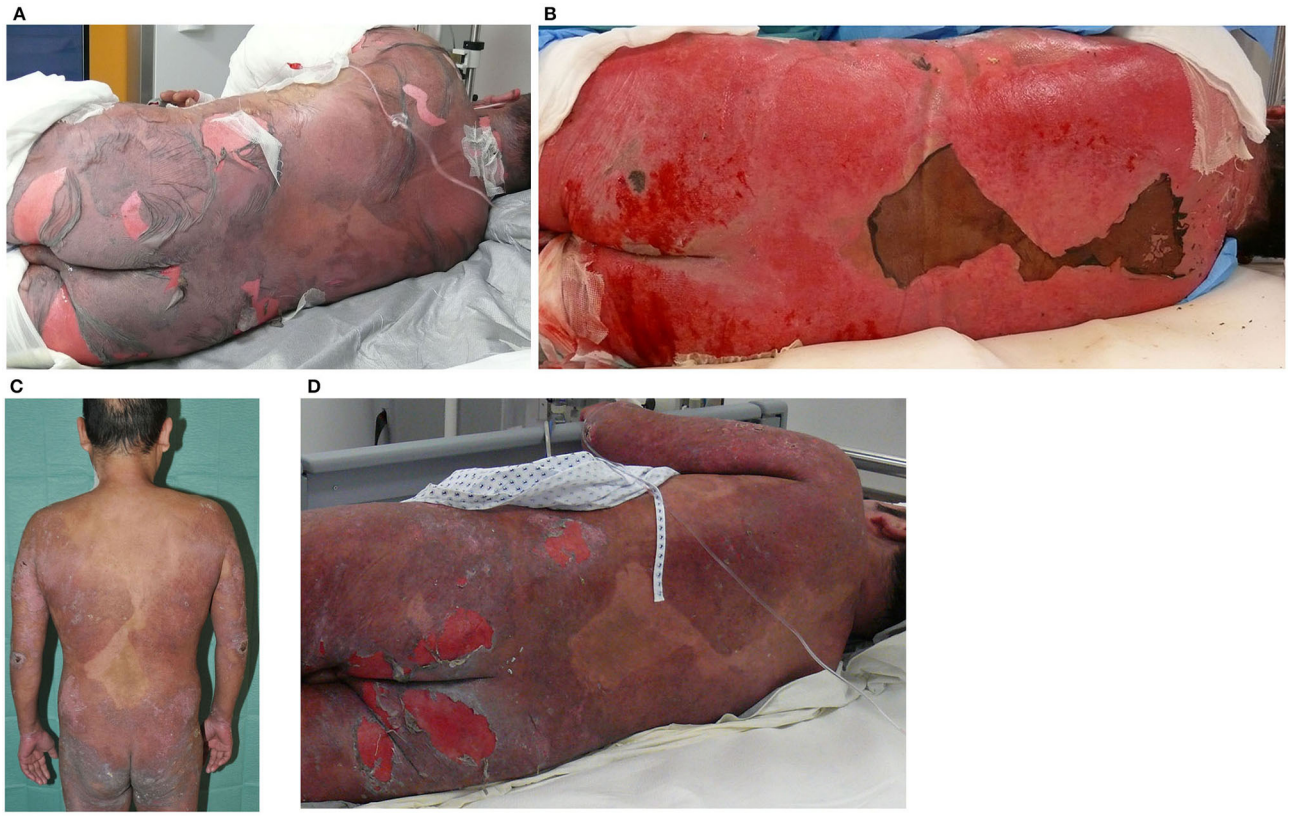

FIGURE 2
Evolution of the severe skin reaction on the back and buttocks. **(A)** Extensive epidermal detachment: large areas of detachable skin without marked erythema or exanthema (10 July 2017); **(B)** healing phase: almost the entire back and buttocks are detached (19 July 2017), **(C)** the previously affected sites heal, leaving well-demarcated residual hyperpigmentation (31 July 2017), and **(D)** epidermal detachment: areas of detachable skin to a lesser extent (3 August 2017) compared to the reaction 1 month before.

chronic florid inflammation, extravasation of erythrocytes and few eosinophils, edema of the dermis, and discrete pigment incontinence. These findings were compatible with erythema multiforme but could not distinguish between bullous FDE and EN through the histomorphological pattern. For treatment of the severe skin reaction, the patient was placed on non-adhesive wound gauze with fusidic acid on erosive lesions, and systemic therapy with 500 mg prednisolone was started. Despite the initiated therapy, the blisters increased within the next few days resulting in large detached areas of the BSA (more than 30%), and the patient was transferred to a burn unit (Figure 2A). Here, he presented with hypotension, tachycardia, catecholamine requirement, and increased fluid loss due to extensive secreting wounds. After transfer, all previously started drugs as well as long-term medication were discontinued. One day later, erosions of oral mucosa and lips were observed. The treatment was performed with daily changes of dressings with polyhexanide and non-adhesive gauze under short-term anesthesia. Furthermore, systemic treatment with ciclosporin (3 mg per kg body weight) for 10 days was started. Because of the extensive skin detachment, it was not possible at this point to distinguish clinically between EN on large erythema and GBFDE. Within the next few days, the progression stopped and re-epithelialization started (Figure 2B), the patient did no longer require catecholamines, and the topical treatment was modified. During the process of wound healing, the pattern became more suggestive for GBFDE because there were clearly demarcated, large brownish patches (Figure 2C).

After 3 weeks at the burn unit, the patient was transferred back to his local hospital in a cardiopulmonary stable condition and with nearly completed re-epithelialization. After 2 days, the patient experienced generalized pain, for which metamizole 10 drops were accidentally administered. One h later, he developed generalized pruritus, which was treated with dimetindene maleate. Shortly after that, the patient complained about vertigo, fever up to 102.2°F (39°C), hypotension, and tachycardia. He was transferred to the intensive care unit, where he developed skin blisters in a generalized distribution. The symptoms aggravated overnight, and consecutively, the patient was again transferred to the burn unit (Figure 2D). There, he presented with a fever of up to 104.9°F (40.5°C), a catecholamine requirement, but cardiopulmonary stable and with less skin detachment than the month before. Residual post-inflammatory hyperpigmentation could be seen. Supportive care and topical treatment were performed as before but without systemic immunomodulating treatment. Progress of the skin reaction stopped immediately with the detachment of ∼10% BSA, the wounds re-epithelialized, and the patient was transferred back to his local hospital after 2 weeks of treatment. After another 4 days, the patient was discharged on 18 August 2017 with a diagnosis

of "GBFDE due to metamizole", which was proven by a second event after accidental re-exposure within a month. Retrospectively, the diagnosis of GBFDE with the detachment of ∼55% BSA for the event in July was confirmed through an independent validation process by dermatologists of the RegiSCAR-group (International Registry of Severe Cutaneous Adverse Reactions to drugs and collection of biological samples).

Whether the event 1 year before was also related to metamizole could not be clarified with certainty. At that time, the patient had been drinking heavily on a daily basis, and his memory was thus not reliable.

3. Discussion

Fixed drug eruption is a delayed type IV hypersensitivity reaction, which occurs secondary to exposure to a causative agent (5, 16). Each re-exposure to the causative drug leads to lesions that usually recur at previously affected sites ("fixed"). New lesions may also appear on previously not affected skin, whereas old lesions may increase in size (1, 5, 8, 16). Re-exposure to the causative drug after an acute event does not necessarily result in a flare-up of previously involved sites. This is known as the refractory period and can last for weeks or months (17). Generalized bullous fixed drug eruption is a rare and severe variant of FDE with blisters and erosions with involvement of at least 10% of the BSA affecting three of the following six anatomic sites: head/neck, anterior and posterior trunk, upper and lower extremities, and genitalia (18, 19). Due to the generalized distribution with skin detachment, GBFDE can easily be misdiagnosed as EN (1, 18, 20). Even A. Lyell, who introduced the term TEN in 1956, had to acknowledge that two of the four TEN cases in his original report had a diagnosis of GBFDE (12, 21).

Distinguishing GBFDE and EN can be a big challenge as demonstrated by our case with skin detachment of more than 50% BSA. Here, the typical well-demarcated, round or oval erythematous or violaceous patches were not seen at first. Usually, this clinical presentation is a clear distinguishing feature from EN, in which typically a confluent exanthema of macules and/or atypical targets is present (2, 6, 22, 23). When the consensus definition for EN was developed, cases without macules and/or atypical targets but skin detachment of more than 10% BSA were identified. For these cases, the category "TEN without spots" or "TEN on large erythema" was proposed (15). The consensus definition was published in 1993, and experts are now debating whether the few reported cases of "TEN on large erythema" were misclassified and are severe cases of GBFDE (13). The evaluation of a biopsy is often not helpful to distinguish between GBFDE and EN. In both diseases, vacuolar interface dermatitis with necrotic keratinocytes and subepidermal blistering is the most common histopathological pattern (6, 18, 22, 24, 25). Histological features are either individual apoptotic keratinocytes up to clusters in a disseminated distribution or complete epidermal necrosis (6, 26, 27). The dermis reveals a sparse superficial perivascular lymphohistiocytic inflammatory infiltrate (6, 18, 24). In a later stage of GBFDE, a deeper perivascular infiltrate with eosinophils and sometimes neutrophils can be seen, but this pattern is not necessarily indicative (6, 18, 28). The infiltration of eosinophils is more suggestive of GBFDE, and when it is seen, the eosinophils occur in a higher number than in EN (18, 20). Melanophages are also more likely to be associated with GBFDE; in particular, they are present in the late stage and in recurrent events, as they persist in the hyperpigmented areas, revealing pigment incontinence in the histology (18, 29, 30).

Traditionally, it is thought that there is no or rather mild mucosal involvement in GBFDE (1, 22). In a retrospective study, it was shown that in cases of GBFDE, mucosal lesions are more likely present compared with less severe cases of FDE (66.7 vs. 30%) (18). Another study demonstrated that mucosa was involved at one site in 67% of GBFDE cases (2). Compared with EN patients, the mucosal involvement in GBFDE is milder, less pronounced, and often limited to one site, but the mucosa is affected in approximately two-thirds of GBFDE cases (2, 18). In more than 90% of EN cases, involvement of mucous membranes is observed in at least two sites (13). Interestingly, in contrast to EN, ocular mucosa does not seem to be affected in GBFDE. Furthermore, fever and reduced general state are less frequent in GBFDE compared to EN, although GBFDE patients are older (2, 4, 18, 25). It is assumed that GBFDE has a better prognosis than EN (8, 22, 31). However, GBFDE is potentially life-threatening as demonstrated in a large retrospective study matching 58 GBFDE patients with 170 EN patients for age and extent of detachment. The mortality rate did not differ between these two conditions (22% for GBFDE vs. 28% for EN), indicating that especially GBFDE in the elderly deserves the same care and supportive treatment as EN (2, 32).

The two diseases can be distinguished not only based on clinical presentation but also based on medical history (6, 16). GBFDE is a "classical allergic reaction" with sensitization of a susceptible person to a particular drug (or additive or food) with a variable incubation period ranging from a few weeks to many years (5, 27). In addition, sensitization to the particular drug occurs faster with intermittent intake than with continuous use (5). With repeated exposure to the causative drug, the lesions usually occur within 30 min to 48 h (5, 6, 32–34). In contrast, EN patients develop the reaction within the first 8 weeks of treatment, with the majority of the causative drugs being taken in the period of 4–28 days before the onset of EN. In addition, it is the first continuous use of the drug, and there are no previously tolerated exposures in the medication history (6, 35, 36). This leads directly to another distinguishing feature: the presence of previous reactions in cases of GBFDE, which may have been localized and non-bullous. A study from Taiwan found that previous reactions were present in two-thirds of GBFDE cases but were absent in EN cases (18). A GBFDE cohort of 62 patients in Germany also showed that ∼62% of the patients had at least one prior event (19). In another study, 38% of the GBFDE patients and 1% of the EN patients reported a previous event (2).

A variety of drugs are associated with FDE. There are geographical differences in the most common causative drugs, sometimes even in the same place over time (1, 26, 29, 37). Anti-infective agents (e.g., ß-lactam antibiotics, tinidazole, and acyclovir), analgesics [e.g., acetaminophen (paracetamol), mefenamic acid, and metamizole], non-steroidal anti-inflammatory drugs (NSAIDs), anti-epileptic drugs (e.g., carbamazepine), psychoactive agents (e.g., barbiturates and codeine), and other miscellaneous drugs (e.g., allopurinol,

TABLE 1 Characteristics of generalized bullous fixed drug eruption and epidermal necrolysis.

	Generalized bullous fixed drug eruption	Epidermal necrolysis
Clinical presentation—skin	Well-demarcated, round or oval erythematous or violaceous patches with blisters/erosion on patches OR Diffuse generalized erythema with flaccid blisters	Confluent exanthema of macules and/or atypical targets with blisters/erosions
Clinical presentation—mucosae	1 site in approximately two-thirds of cases (oral, urogenital) Mild and less pronounced	≥2 sites in >90% (oral, ocular, urogenital, and nasal)
Fever and reduced state of health	Less frequent	More frequent
Histological findings	Vacuolar interface dermatitis Necrotic keratinocytes (individual to full-thickness) Sparse to dense inflammatory infiltrate Eosinophils more frequent Melanophages more frequent	Vacuolar interface dermatitis Necrotic keratinocytes (individual to full-thickness) Sparse inflammatory infiltrate Eosinophils rarely present Melanophages rarely present
Latency period (onset after drug intake)	30 min to 48 h	4–28 days
Previously tolerated exposures	Yes, reaction occurs faster with intermittent intake of the culprit drug	No, first continuous use
Previous similar (localized) reaction(s)	Present in up to two-thirds of cases Same-site recurrence with an increase in size and detachment Faster with each recurrence	Present in ≤ 1% No increase in size and detachment Latency stays the same
Testing	Provocation test contraindicated due to the severity of the disease Patch test up to 80% correct positive	Provocation test contraindicated due to the severity of the disease Patch test < 25% correct positive

contrast media, omeprazole, and loratadine) are associated with FDE (7, 18, 26, 38). However, the most common cause of any type of FDE over a long period was the anti-infective drug trimethoprim–sulfamethoxazole, as shown in various studies from different countries (27, 29, 37, 39–42). With decreased use of this sulfonamide combination drug since the 2000s, it has been replaced by naproxen as the most common cause of FDE in Turkey (43). Analgesics are now also identified as the most common cause in many other countries: for example, mefenamic acid in Taiwan (32) and Tunisia (33); etoricoxib, NSAIDs, and acetaminophen (paracetamol) in Singapore (44); and acetaminophen (paracetamol) and NSAIDs in Korea (45). Metamizole is also a known inducer of FDE, with most reports being published before 2000 (37, 46, 47). In recent years, only individual cases of severe GBFDE associated with metamizole were reported (4, 9), which could lead to the impression that the overall number of cases has decreased substantially (29). However, it is striking that a few of the published metamizole-related EN cases more likely seem to be cases of GBFDE, based on the history and the description of the clinical presentation (48–50). The impression that metamizole appears less frequently as a highly suspicious cause can be explained by the fact that it has been withdrawn from the market or never got approved in many countries (e.g., Australia, France, Singapore, and the United States), while in other countries (e.g., Germany, Spain, and Switzerland), it is only available by prescription (51). Nevertheless, in Germany, for example, the number of prescriptions of metamizole almost doubled between 2008 and 2017 leading to an increase of non-allergic and allergic hypersensitivity reactions (52). In many countries (e.g., China, Mexico, Russia, and Turkey), metamizole can be purchased over the counter (51). Due to multiple medications, the causative drug could not be identified in about a quarter of the cases in two studies from Iran and Taiwan (18, 42). Earlier studies have demonstrated that the causative drug could be identified by oral challenge in most cases of GBFDE but not in EN (3, 53). Furthermore, the reaction to the oral re-challenge was completely different between these two diseases. EN could only be provoked in ∼10% of the cases by re-challenge with the causative drug but induced discomfort and/or a milder rash. In contrast, GBFDE patients most often reacted to re-challenge with the same pattern (12, 53). Therefore, the oral provocation test is contraindicated in both GBFDE and EN. It is rarely performed even in localized FDE to not trigger GBFDE (1, 54). A patch test is considered safe but less sensitive. Patch testing in FDE or GBFDE is recommended to be performed in previously involved hyperpigmented skin areas if the localization permits. If not, it can be performed as usual on the patient's back. The response rate varies among different studies from 33% to ∼80% (18, 33, 55). Therefore, an exact medication history is essential and should also include herbal remedies, over-the-counter medications, and food (6, 38). On the contrary, a patch test is not helpful in EN, since correct positive results are achieved in <25% of the tests (56). Table 1 summarizes the characteristics of both diseases.

For treatment, the first step is the identification and removal of the causative drug. Since FDE is a self-limiting disease, supportive therapy is the gold standard and should be adapted according to severity (6, 26, 29).

A case of GBFDE with the detachment of more than 50% BSA is very rare, especially considering that GBFDE itself is a rare and severe variant of FDE and that such a condition can be easily misdiagnosed as EN is reasonable. However, GBFDE and EN are two entities with differences in (1) general condition, (2) clinical presentation, (3) latency period between the beginning of drug use and reaction onset, (4) previous intake, (5) history of previous

similar (localized) reaction(s), and (6) pathogenesis. GBFDE is a severe disease that may lead to more extensive skin detachment with each recurrence and deserves the same care and supportive treatment as EN.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual's primary caregiver for the publication of any potentially identifiable images or data included in this article.

Author contributions

MP drafted the original manuscript. FR, MM, and ML revised the manuscript. All authors approved the final manuscript as submitted for publication.

Acknowledgments

The authors acknowledge the Open Access Publication Fund of the University of Freiburg for supporting the publication of this research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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