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Cutaneous vasculitis: Lessons from COVID-19 and COVID-19 vaccination

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Cutaneous vasculitis (CV) is an inflammatory skin-limited vascular disease affecting the dermal and/or hypodermal vessel wall. From the pathogenetic point of view, idiopathic forms are described as well as the induction from various triggers, such as drugs, infections, and vaccines. Following SARS-CoV-2 pandemic outbreak, cases of CV induced by both COVID-19 and COVID-19 vaccinations have been reported in literature. The aim of our work was to collect multiple cases available in the literature and analyze the frequency of the different forms of induced vasculitis, as well as their histological and immunopathological features. Although rare, CV induced by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and vaccines may provide interesting insights into the pathogenesis of these inflammatory processes that may in the future be useful to understand the mechanisms underlying cutaneous and systemic vasculitis.

KEYWORDS

vasculitis, cutaneous vasculitis, COVID-19, leukocytoclastic vasculitis, IgA vasculitis, urticarial vasculitis, COVID-19 vaccines, vaccine-induced vasculitis

Introduction

The term vasculitis encompasses a wide and heterogeneous group of disorders with shared histopathological findings. It is a pathological process characterized by an inflammatory process affecting the vessel wall, both arterial and venous, of different sizes and of any body area (1). Inside the vessel wall, there is an infiltrate, which can create discontinuity of the wall itself with red blood cells leaking. One of the most successful attempts at proper classification of such condition has been proposed by the 2012 Chapel Hill consensus cVonference nomenclature of vasculitides (CHCC 2012) (2), which divides them according to the diameter of the affected vessel: Large Vessel Vasculitis and Medium Vessel Vasculitis, which in the skin can cause necrosis and ulceration and livaedo reticularis; Small Vessel Vasculitis, manifesting with purpura and vesiculo-bullous lesions.

Since the skin is one of the most affected organs in vasculitides, in 2018, a Dermatological Addendum has been suggested to further help the clinician in dealing with such conditions, improving the definition of some forms of cutaneous vasculitis (CV) and adding other dermatological relevance (3). Accordingly, CV may be a cutaneous manifestation of systemic vasculitis or a skin-limited or skin-dominant variant of systemic vasculitis, but when affecting only the skin in the absence of any other systemic involvement, the term single-organ vasculitis (SOV) should be used.

CV is mainly a small-vessel vasculitis affecting dermal and/or hypodermal capillaries and venules, which usually show histopathologic findings consistent with leukocytoclastic vasculitis, characterized by fibrinoid necrosis of vessel wall, erythrocyte extravasation, and neutrophilic infiltrate with degeneration known as leukocytoclasis with nuclear dust (karyorrhexis) (4). The immune infiltration may be mainly lymphocytic in lesions that appeared more than 48 h before. Direct immunofluorescence (DIF) of lesional skin is helpful in the diagnosis of CV, with maximum efficacy for the diagnosis of IgA vasculitis and lupus vasculitis. It can aid in the accurate diagnosis even when the histological changes are minimal (5–7). However, DIF positivity is strongly influenced by the timing of the biopsy (8).

Even though in more than half cases of CV it is impossible to assess the disease-inducing or promoting factor, it is well-known that the most common triggering factors are related to immunopathogenic mechanisms secondary to infections or drug intake (9, 10). Therefore, it is not surprising that since the beginning of the COVID-19 pandemic and after the introduction and administration of COVID-19 vaccines on a global scale, cases of COVID-19-associated and vaccine-associated CV have been reported (11–13).

When involving the skin, clinical manifestations of the COVID-19 infection show a great range of signs and symptoms (14). Five major classes of cutaneous manifestations in the setting of COVID-19 infection have been proposed by Tan et al. (15), e.g., pseudo-chilblains lesions, urticarial rash, vesicular (varicella-like) eruption, maculo-papular rash, and vaso-occlusive lesions. Several cases of both new onset and flares of CV have also been linked to COVID-19 and SARS-CoV-2 vaccination. However, they are not included in the aforementioned classification due to their low frequency (12, 16, 17).

Similarly, many heterogeneous cutaneous reactions to COVID-19 vaccination have been reported and classified by Shakoei et al. into the following major categories: local site reactions, type 1 (immediate) hypersensitivity reactions, type 4 (delayed) hypersensitivity reactions, autoimmune-mediated reactions, functional angiopathies, and reactivation of other viral conditions (18). In this classification, CV are classified among the auto immune-mediated reactions. Most of the cases reported occurred after the administration of messenger ribonucleic acid (mRNA)-based vaccines (19). In the literature, vaccine-associated CVs have been more frequently reported than CVs secondary to the COVID-19 infection. The number of persons that received at least one dose of the vaccine worldwide is larger when compared to that of the persons who contracted the infection. However, it is known that the vaccine reproduces only a small degree of adverse effects provoked by the natural infection of the immune system. Therefore, more vaccine-associated CVs are diagnosed and reported due to the greater attention that has been given by patients to all the side effects related to the COVID-19 vaccine.

In this review, we analyze and compare the current and most recent literature on clinical and immunohistopathologic features of CV induced by systemic SARS-CoV-2 infection and CV secondary to the SARS-CoV-2 vaccine, focusing on the possible underlying pathogenetic mechanisms.

SARS-CoV-2 infection and cutaneous vasculitis

We collected clinicopathological features of a series of CV that occurred in association with the SARS-CoV-2 infection available in the literature (Table 1). Our search was restricted to cases with histological confirmation of leukocytoclastic vasculitis. Totally, 19 cases were included, mostly males (13/19) with variable age distribution ranging from 13 to 93 years with an average of 48.4 years. In three cases, the diagnosis was COVID-19-associated IgA vasculitis, while in five cases the patients had been diagnosed with COVID-19-associated urticarial vasculitis; finally, the other cases may be considered as cutaneous leukocytoclastic vasculitis associated with COVID-19, being not further classified according to the Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (3). Regarding the clinical presentation, a comparison between the frequency of different types of lesions did not reveal feasible given the heterogeneity of their description. However, it is reasonable to consider palpable purpura as the main clinical manifestation, sometimes with necrotic features and hemorrhagic blistering. The most common sites affected were the lower limbs and trunk, as for the idiopathic forms of CV. The cases diagnosed with urticarial vasculitis showed slight clinical differences, since skin lesions were characterized by wheals or urticarial manifestations, associated with purpuric aspects. The edematous component of cutaneous lesions in COVID-19-associated urticarial vasculitis was appreciable at histological evaluation in 2 out of 5 cases, whose report mentioned dermal or endothelial swelling. The latency time between skin rash occurrence with SARS-CoV-2 infection is highly variable, ranging from concomitant signs appearing at the time of onset to more than 30 days after the first positive nasopharyngeal swab. The totality (3/3) of COVID-19-associated IgA vasculitis cases presented kidney involvement, but it is of interest that in

two out of three cases, the direct immunofluorescence (DIF) performed on lesional skin resulted negative while positivity was seen in all three cases when performed on kidney biopsy. Although based on a few cases, our results are in accordance with Jedlowski *et al.*, which published a case series of 10 subjects with COVID-19-associated systemic IgA vasculitis; in fact, authors found positive skin DIF in less than half of the series (40%) while kidney biopsies showed IgA deposition in all the cases. Moreover, it is of note that COVID-19-associated IgA vasculitis more commonly affects adults when compared to the classical form of IgA vasculitis in which 90% of cases occur in the pediatric population. In our series, one DIF resulted non-specifically positive for C3, while in nine cases, it was negative for all the reactants. No cases of cutaneous IgG/IgM vasculitis were diagnosed and in eight subjects DIF was not performed. Interestingly, three cases assessed the colocalization of SARS-CoV-2 in the vessel wall, finding positivity in 2/3 cases by the PCR technique. This may support the direct role of SARS-CoV-2 in the pathogenesis of cutaneous vasculitis and its tropism for a broad variety of human tissues.

SARS-CoV-2 vaccination and cutaneous vasculitis

In the mini-series presented (Table 2), only patients with histological confirmation of leukocytoclastic vasculitis were included. Totally, 39 patients developed CV after the COVID-19 vaccine. Women were found to be more involved than men, counting 24 females vs. 15 males developing CV. The weighted average of the patients reported was of 53.2 years (range 22–94).

Clinically, purpuric papules or maculae in the lower extremities were the most commonly reported skin manifestation (Figure 1). DIF was not reported in 21 cases (53.8%) and in 5 cases (12.8%) it was negative. Features were heterogeneous in the remaining 13 cases, with 5 cases (12.8%) of IgA vasculitis and 3 cases (7.7%) of vasculitis with C3 deposition, and some isolated cases of IgM vasculitis with fibrinogen deposit.

Most of the reported cases (n = 19, 48.7%) were associated with mRNA vaccines; particularly, 13 patients underwent BNT162b2 [BioNTech/Pfizer] vaccines and five patients underwent mRNA-1273 [Moderna] vaccines. In one case, the commercial name of the vaccine was not reported. Eleven cases (28.2%) of CV were associated with adenoviral vector-based vaccines, of whom 10 were with ChAdOx1 nCoV-19 [Oxford-AstraZeneca] and one was with Ad26.Cov2.S [Johnson & Johnson].

Among the nine cases (23.1%) associated with inactivated vaccines, only one was not named, three cases were found after the administration of both Covaxin and Sinovac, and two cases after Sinopharm administration.

Nineteen patients (48.7%) developed CV after the first dose of the vaccine, while 16 (41%) after the second dose; only 3 (7.7%) cases were reported to occur after the third dose of the vaccine injection. In one case (2.6%), the dose number was non-specified.

Discussion

Our review reported the main aspects of both CVs induced by COVID-19 infection and vaccines. Only leukocytoclastic vasculitis was included, and DIF pattern was also analyzed. Unfortunately, in many of the reported cases, DIF was not conducted, while some cases were negative. Its evaluation is extremely important in defining the type of CV and DIF positivity may raise the suspicion of systemic disease, providing useful prognostic information where histology alone cannot. Therefore, DIF should be always performed especially on early lesions because immune deposits may disappear in lesions that occurred more than 48 h before.

To date, the exact pathogenetic mechanisms underlying COVID-19-associated CV have not been fully understood. Since its outbreak in 2019, COVID-19 had spread all over the world causing a global pandemic affecting more than 500 million people and at least 6 million deaths (20). The enveloped RNA virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiologic agent, which primarily affects the respiratory tract leading to general symptoms like fever, fatigue, anosmia, and dysgeusia, while respiratory symptoms are variable in severity ranging from cough and rhinorrhea to dyspnea, pneumonia, or acute respiratory distress syndrome. However, evidence about the involvement of other organs and systems is increasing; in fact, knowledge about the neurological, gastrointestinal, and ocular manifestations of SARS-CoV-2 infection is deepening (21, 22). Similarly, cutaneous signs of COVID-19 are continuously reported and attempts at classifications are already available in the literature, together with the first prevalence estimations in which dermatologic manifestations would place between 1.8 and 20.4% of the COVID-19 patients (23, 24). In particular, several works identified clusters of skin manifestations that are suggestive of skin vascular damage, namely chilblain-like lesions, acral ischemia, acral vasculitis, livedo reticularis, livedo racemosa, purpuric "vasculitic" rash, or petechial eruptions (25–27). While a definitive nomenclature is justifiably actually lacking, considering the novelty of these entities, it is well known that SARS-CoV-2 features a markable tropism for endothelial cells. The first hypothesis of vascular damage provoked by the novel coronavirus was provided from autoptic studies showing platelet-fibrin thrombi in lung blood vessels in patients who died of severe COVID-19 (28), advancing the evidence of coagulopathy as a main pathogenetic mechanism of single- or multiorgan damage induced by SARS-CoV-2. Indeed, the term "immunothrombosis" is now used to refer to the typical pattern of lung damage resulting from massive viral-induced inflammation, which leads to the activation

TABLE 1 Clinical, histological, and immunological findings in patients with COVID-19-associated CV.

Case no	Age	Sex	Comorbid	Time to infection	Clinical presentation	Histology	DIF	SARS-CoV-2 in dermal vessels	Ref
1	93	M	CKD PAD Hypertension	8 days	purpuric macules and papules on legs, hands, and periumbilical area	Fibrin deposition, Obliteration of vessels Extravasated red blood cells	Negative for IgG, IgA, IgM, C3	N/A	Capoferri et al. (45)
2	66	M	T2DM Hypertension CAD	15 days	Palpable purpuric papules with necrotic center Maculo-papular lesions on legs and forearms	Fibrin extravasation in vascular structures Inclusion bodies in endothelial cells Perivascular neutrophil, lymphocyte infiltrate Leukocytoclasis in the dermis	Negative for IgG, IgM, IgA, C3	N/A	Bay et al. (46)
3	16	F	None	N/A	Edematous, maculopapular erythematous rash on extremities, abdomen, back, thighs and face	Neutrophilic vasculitis Karyorrhectic debris Focal degeneration of vessel wall Rare intraluminal fibrin deposits Micro-thrombi	Negative for IgG, IgM, IgA, C3	N/A	Gosnell et al. (47)
4	13	M	None	28 days	Petechial and purpuric rash on both feet and ankles	Superficial epidermal necrosis	Negative for IgG, IgM, IgA, C3	Positive (PCR)	Kumar et al. (48)

(Continued)

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TABLE 1 (Continued)

Case no	Age	Sex	Comorbid	Time to infection	Clinical presentation	Histology	DIF	SARS-CoV-2 in dermal vessels	Ref
						Small-vessel neutrophilic vasculitis			
5	32	F	Crohn disease	14 days	Erythematous to violaceous macules and papules on lower extremities and dorsum of feet	Perivascular karyorrhectic material Stromal edema and purpura Capillary ectasia Thrombotic vasculopathy	Not performed	N/A	Nassani et al. (49)
6	49	M	None	14 days	Palpable purpura on inferior limbs and abdomen	Hyperkeratosis Moderate neutrophilic infiltration Extravasated red blood cells Lymphocytes around dermal vessels	Not performed	N/A	Iraji et al. (50)
7	70	M	None	N/A	Palpable petechiae on dorsal feet, thighs, abdomen Purpuric plaques	Leukocytoclastic vasculitis	Positive for IgA	N/A	Jedlowski et al. (51)
8	27	M	None	N/A	Painful purpuric papules Vesicobullous hemorrhagic lesions Necrotic lesions	Leukocytoclastic cutaneous vasculitis Microthrombi	Negative for IgG, IgM, IgA, C3	N/A	Gouveia et al. (52)
9	43	M	Hypertension	N/A	Painful hemorrhagic bullae	Leukocytoclastic vessel vasculitis	Negative for IgG, IgM, IgA, C3	N/A	Kösters et al. (53)

(Continued)

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TABLE 1 (Continued)

Case no	Age	Sex	Comorbid	Time to infection	Clinical presentation	Histology	DIF	SARS-CoV-2 in dermal vessels	Ref
					Necrotic lesions on trunk, arms, legs	Neutrophilic infiltration Eosinophils and histiocytes			
10	29	M	None	28 days	Purple palpable papules Necrotic lesions Serohaematic blisters on abdomen, buttocks, lower legs, feet	Heavy neutrophilic infiltrate in small vessel wall Leucocytoclasis Fibrinoid necrosis Extravasation of red blood cells	Negative for IgG, IgA, IgM, C3	Positive (PCR)	Camprodon Gómez et al. (54)
11	47	M	Hypertension, impaired glucose tolerance	18 days	Multiple, raised erythematous wheals, alone or in cluster, some with central purple Hyperpigmentation on head, trunk and upper arms	Orthokeratotic hyperkeratosis Spongiosis Focal lymphocytic exocytosis Perivascular neutrophilic infiltration Vessel wall damage	Not performed	N/A	Skroza et al. (55)
12	64	F	Hypertension, T2DM	Concomitant	Annular and polycyclic urticarial lesions with purpuric component on trunk and limbs	Dermal edema Leukocytoclastic vasculitis	Not performed	N/A	Nasiri et al. (56)
13	59	M	N/A	35 days	Maculopapular purpuric exanthema on face, trunk, limbs	Perivascular neutrophilic infiltrate	Not performed	N/A	Caputo et al. (57)

(Continued)

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TABLE 1 (Continued)

Case no	Age	Sex	Comorbid	Time to infection	Clinical presentation	Histology	DIF	SARS-CoV-2 in dermal vessels	Ref
						Leucocytoclasis Red blood cell extravasation Fibrinoid necrosis of vessel walls			
14	N/A	F	N/A	N/A	Painful erythematous patches on trunk, hips	Red blood cell extravasation	Not performed	N/A	de Perosanz-Lobo et al. (58)
					Purpura	Neutrophilic perivascular inflammation Karyorrhexis			
15	N/A	M	N/A	N/A	Erythematous and edematous plaques with a purpuric center	Perivascular neutrophilic inflammation Red blood cell extravasation Endothelial swelling Necrotic lesions Fibrin deposition	Not performed	N/A	de Perosanz-Lobo et al. (58)
16	79	F	N/A	7 days	Purpuric macules and papules on legs	Fibrinoid necrosis of vessel walls Transmural infiltration by neutrophils Karyorrhexis Leukocytoclasia Red blood cell extravasation	Positive for C3	Negative (PCR)	Dominguez-Santas et al. (59)

(Continued)

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TABLE 1 (Continued)

Case no	Age	Sex	Comorbid	Time to infection	Clinical presentation	Histology	DIF	SARS-CoV-2 in dermal vessels	Ref
17	83	F	Hypertension TIA AF CKD	30 days	Purpuric palpable papules and serohematic blisters on lower legs, feet, toes	Perivascular neutrophils Fibrins in vessel wall of the dermis Leukocytoclasia	Not performed	Not performed	Mayor-Ibarguren et al. (60)
18	30	M	No	Concomitant	Painful purpuric rash	Leukocytoclastic vasculitis	Negative for IgA, IgG, IgM, C3	Not performed	Li et al. (61)
19	22	M	None	Concomitant	Palpable purpura with central vesicles on extremities, gluteal region, lower abdomen	Perivascular infiltrate of neutrophils, lymphocytes Red blood cell extravasation Fibrinoid necrosis of vessel wall	Negative for IgG, IgM, IgA, C3	Not performed	Sandhu et al. (62)

CKD, chronic kidney disease; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; TIA, transient ischaemic attack; AF, atrial fibrillation.

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TABLE 2 Clinical, histological, and immunological findings in patients with COVID-19-vaccine associated CV.

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
1	30	M	Adenoviral vector-based	Johnson-Johnson	Negative nasopharyngeal RT-PCR swab	None	17 days after the first dose	Painful hemorrhagic papules and vesicles on soles, shins, elbows	Mild proteinuria Hypocomplementemia Cryoglobulinemia	Granular deposits of IgM, C3, and fibrin/fibrinogen in the walls of the dermal small vessels	Betetto L et al. (63)
2	45	M	Inactivated vaccine	Sinopharm	Not mentioned	None	2 days after the first dose	Papular lesions on upper and lower limbs	Pruritus	Not performed	Shakoei et al. (18)
3	61	F	Adenoviral vector-based	Oxford-AstraZeneca	Negative nasopharyngeal RT-PCR swab	Hypertension	5 days after the first dose	Pruritic erythematous-purpuric macules involving the lower legs, feet, buttocks, axillae, abdomen	Myalgia Fatigue	Not performed	Criado et al. (13)
4	52	M	m-RNA-based	Moderna	Not mentioned	Not mentioned	11 days after the second dose	Erythematous, non-pruritic petechial rash on lower limbs	Not reported	Not performed	Gázquez Aguilera et al. (11)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
5	80	M	m-RNA-based	BioNTech/Pfizer	Negative serologic investigations	Psoriasis	4 weeks after the second dose	Targetoid erythematous lesions	Fever	Negative for IgG, IgM, IgA, C3	Wollina et al. (19)
									Fatigue General malaise		
								Necrotic lesions on legs Erythematous lesions on the soft palate			
						Hemochromatosis Nodular goiter					
								Purpuric macules on fingers and palmar creases Splinter hemorrhages on nails			
6	57	F	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	Fibrocystic mastopathy	5 days after the second dose	Purpuric macules and papules on lower legs	Not reported	Linear and granular deposition of IgM within small vessels	Fiorillo et al. (64)
						Hypertension					

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
7	51	F	m-RNA-based	Moderna	No prior history of SARS-CoV2 infection	Sjögren syndrome Cryoglobulinemic vasculitis	3 weeks after the second dose	Palpable purpura and ulcers Lower extremities pitting edema	Acute kidney injury Nephrotic syndrome	Not performed	Vornicu et al. (65)
8	59	F	m-RNA-based	BioNTech/ Pfizer	No prior history of SARS-CoV2 infection	Sjögren syndrome Cryoglobulinemic vasculitis	2 days after the first dose	Palpable purpura Small cutaneous malleolar ulcers	Fatigue Fever Myalgias Acute kidney injury Nephritic syndrome	Not performed	Vornicu et al. (65)
9	55	F	Adenoviral vector-based	Oxford-AstraZeneca	Negative RT-PCR	None	5 days after the first dose	Palpable purpura on lower limbs	Fever Myalgia Wrist swelling	Negative	Sandhu et al. (66)
10	48	M	Adenoviral vector-based	Oxford-AstraZeneca	Negative RT-PCR	Hypertension	2 days after the second dose	Palpable purpura on hands, forearms, gluteal region, lower limbs	Fever Myalgia	Negative	Sandhu et al. (66)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
11	46	F	m-RNA-based	BioNTech/Pfizer	Not mentioned	Psoriasis PsA Irritable bowel syndrome Leukocytoclastic vasculitis	2 days after the first dose (1st flare), 2 days after the second dose (2nd flare)	Exacerbation of palpable purpuric papules lower legs (first flare) Palpable purpuric papules on the lower legs, feet, upper extremities, lower back, and abdomen (second flare)	Not reported	Not performed	Cohen et al. (67)
12	83	F	m-RNA-based	BioNTech/Pfizer	Not mentioned	None	5 days after the second dose	Palpable purpura with erythema and edema on lower extremities	Elevated levels of C-reactive protein, elevated sedimentation rate, Rheumatoid factor Hypocomplementemia	Deposition of fibrinogen around superficial blood vessels	Larson et al. (68)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
									Cryoglobulinaemia		
13	57	F	m-RNA-based	Not mentioned	Not mentioned	Epilepsy Bipolar disorder Depression	7 days after the first dose	Erythematous confluent papules and plaques involving trunk, extremities	Not reported	Not performed	Bostan et al. (69)
14	46	F	Inactivated	Covaxin	Negative oro-nasopharyngeal RT-PCR swab	None	5 days after the first dose	Palpable purpura on legs Pitting edema on ankles	Arthralgia Ankle swelling	Not performed	Kar et al. (44)
15	47	M	m-RNA-based	BioNTech/Pfizer	Not mentioned	Intermittent abdominal pain	3 days after the first dose (first episode); 4 days after the second dose (flare)	Reddish spots in his ankles (first episode) Purpuric papules on legs, forearms (second episode)	Elevated C-reactive protein Proteinuria Decreased glomerular filtration rate	C3/C4 deposits	Gambichler et al. (70)
16	59	F	m-RNA-based	Moderna	Not mentioned	Hypertension Hyperlipidemia	1 day after the second dose	Violaceous petechiae on legs, pelvis, abdomen, upper limbs	Intermittent abdominal pain	Not performed	Ireifej et al. (71)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
									Elevated C-reactive protein		
						Prediabetes Obesity COVID-19 in April 2020					
17	57	F	Inactivated	Sinopharm	Not mentioned	None	5 days after the second dose	Purpuric papules with central blistering Necrotic lesions Black eschars on legs Palpable purpura on thighs, buttocks, abdomen, back, forearms	Fatigue Arthralgia	Not performed	Azzazi et al. (39)
18	94	M	m-RNA-based	Moderna	Not mentioned	AF	10 days after the second dose	Palpable purpura	Not reported	IgA immune deposits in the blood vessel walls	Grossman et al. (72)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
						Aortic valve replacement Hypothyroidism Anemia					
19	76	M	m-RNA-based	BioNTech/Pfizer	Not mentioned	Liver cirrhosis Heart failure Previous gastroesophageal junction cancer and prostate cancer	12 days after the second dose	Pruritic purpuric macules on hands, feet, legs, thighs, abdomen	Bloody diarrhea	Not performed	Mücke et al. (73)
20	65	M	m-RNA-based	BioNTech/Pfizer	Not mentioned	T2DM Hypertension	2 days after the third dose	Purpuric palpable lesions on legs	Not reported	Not performed	Dicks et al. (74)
21	50	M	m-RNA-based	BioNTech/Pfizer	Not mentioned	None	2 days after the second dose	Rash on the legs	Not reported	IgA-dominant immune deposits in the blood vessel walls	Mohamed et al. (75)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
22	40	F	m-RNA-based	BioNTech/Pfizer	Not mentioned	Hashimoto's thyroiditis	20 days after second dose	Purpuric rash on gluteal region	Headache	Not performed	Hines et al. (76)
23	57	M	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	Hypertension	14 days after the first dose	Purpura on lower limbs, abdomen, trunk, head	Not reported	Not performed	Cavalli G et al. (77)
24	57	F	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	Hypertension Hypothyroidism	5 days after the first dose	Palpable purpura on buttocks, legs, arms	Not reported	Negative for IgG, IgM, IgA, C3	Guzmán-Pérez et al. (78)
25	77	F	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	None	10 days after the first dose	Palpable indurated purpuric papules Erythematous plaques and bullae on lower limbs, hands. Purpuric lesions on soft palate, tongue	Not reported	Negative for IgG, IgM, IgA, C3	Shahrigharahkoshan et al. (79)
26	68	F	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	None	7 days after the first dose	Erythematous to purpuric non-blanching macules on lower extremities	Not reported	Not performed	Jin et al. (80)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
27	60	F	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	Chronic liver disease Portal hypertension Polycythemia vera Hypothyroidism T2DM	11 days after the second dose	Painful purpuric lesions on lower limbs	Not reported	IgA and IgM deposits on the walls of postcapillary vessels	Fritzen et al. (81)
28	76	F	Adenoviral vector-based	Oxford-AstraZeneca	Not mentioned	None	7 days after the first dose	Maculopapular rash on lower extremities	Hematuria Arthralgia	Not performed	Sirufo MM et al. (43)
29	46	F	Inactivated	Covaxin	Negative oropharyngeal RT-PCR swab	None	5 days after the first dose	Purpuric papules on legs	Arthralgia Ankle swelling	Not performed	Kar et al. (44)
30	31	F	Inactivated	Covaxin	Negative oropharyngeal RT-PCR swab	None	4 days after the second dose	Palpable purpura on left leg Pitting edema	Not reported	Not performed	Kharkar et al. (82)
31	77	M	Adenoviral vector-based	Sinovac	Negative nasopharyngeal RT-PCR swab	None	2 weeks after the third dose	Palpable violaceous patches	Gastrointestinal involvement (abdominal pain, stool tests on occult blood-positive)	Negative for IgG, IgM, IgA, C3	Oskay et al. (83)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
								Bullous hemorrhagic lesions on lower limbs, hands			
32	33	M	Adenoviral vector-based	Not mentioned	Mildly symptomatic COVID-19 three months before	None	3 days after the first dose	Violaceous eruption	Not reported	IgA deposition within small vessel walls	Bostan et al. (84)
								Erythematous macules Palpable papules on legs, forearms			
33	91	F	m-RNA-based	BioNTech/Pfizer	No evidence of acute SARS-CoV-2 infection	Dementia Hypertension T2DM	4 days after the third dose	Palpable purpuric lesions on lower limbs	Not reported	Not performed	Carrillo-Garcia et al. (37)
34	38	M	m-RNA-based	BioNTech/Pfizer	Not mentioned	None	4 days before the first dose	Purpuric-erythematous macules, papules, and plaques on lower limbs	Arthralgia	Not performed	Altun et al. (36)
35	52	M	m-RNA-based	Moderna	Not mentioned	Not mentioned	11 days after the second dose	Erythematous, non-pruritic rash on legs	Not reported	Not performed	Gázquez Aguilera et al. (11)

(Continued)

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TABLE 2 (Continued)

Case no	Age	Sex	Vaccine type	Vaccine name	Exclusion of SARS-CoV-2 infection	Comorbid	Temporal relation to the vaccine	Clinical characteristics of CV reported	Systemic involvement	DIF	References
								Petechiae on lower limbs			
36	42	F	m-RNA-based	BioNTech/Pfizer	Not mentioned	Hypertension Obesity	4 days after injection (dose number non-specified)	Cutaneous eruption on lower limbs, gluteal area	Not reported	Not evaluable	Erler et al. (85)
37	22	F	m-RNA-based	BioNTech/Pfizer	Not mentioned	None	7 days after the second dose	Small, red, raised, itchy lesions on legs. Purpuric lesions on lower limbs	Not reported	Not performed	Ripalta Colia et al. (38)
38	23	F	Inactivated	Sinovac	Not mentioned	None	36 h after first dose	Non-blanchable erythematous plaques with purpura on extremities	None	C3 and fibrinogen deposition around blood vessel walls	Bencharattanapet al. (86)
39	26	F	Inactivated	Sinovac	Not mentioned	None	4 h after first dose	Non-blanchable purpuric purpura on extremities	None	IgM, C3, and IgA deposition	Bencharattanaphakhi et al. (86)

CKD, chronic kidney disease; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; TIA, transient ischaemic attack; AF, atrial fibrillation.

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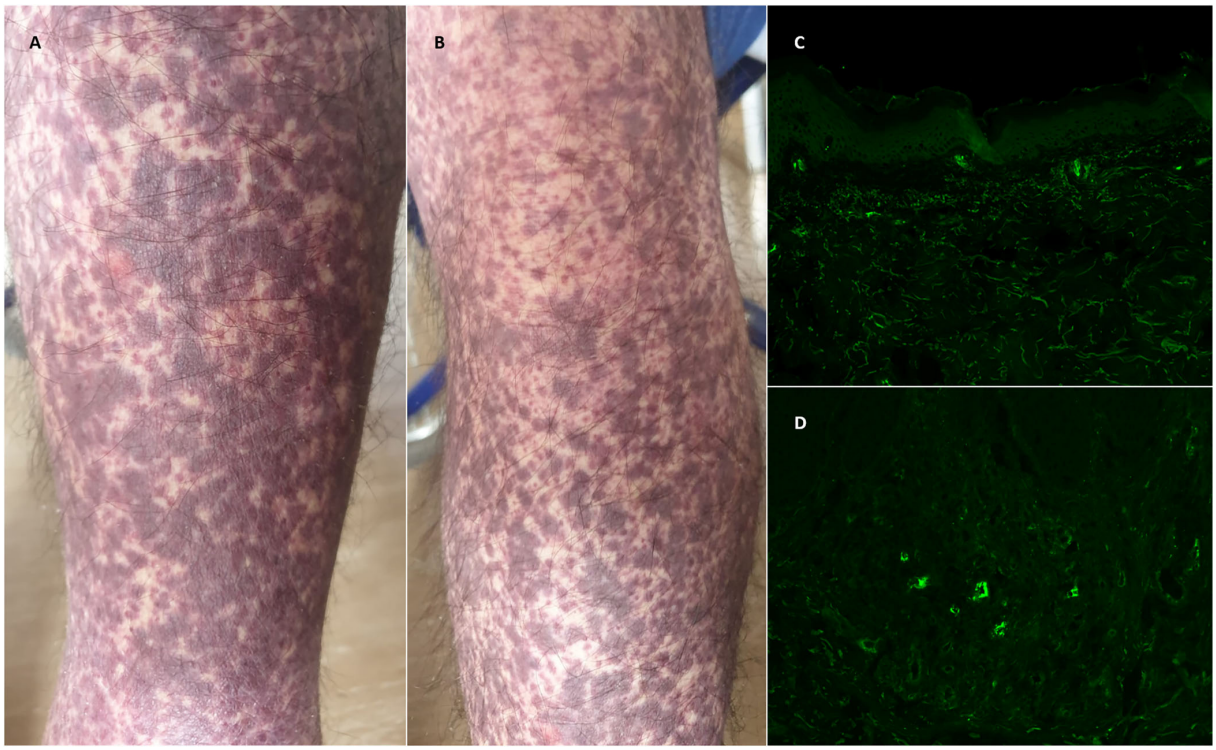

FIGURE 1
(A,B) Purpuric maculae and papules in the lower extremities in a patient with a recent anamnesis of COVID-19 vaccination. **(C,D)** Direct immunofluorescence performed on lesional skin, with evidence of perivascular deposition of C3. (c: 10% magnification, d: 20% magnification).

of the endothelium and triggers intravascular coagulation. Similar mechanisms may be responsible for skin manifestations reflecting vascular dysfunction or true vasculitis, since it was demonstrated that ACE2 is expressed in the skin basal cell layer, dermal vessels endothelium, eccrine glands, and subcutaneous fat tissue and act as a receptor for SARS-CoV-2 Spike protein binding (29). Viral uptake precludes the ACE2-dependent protective action of angiotensin 1–7 and results in oxidative stress, inflammatory cytokine production, and vasoconstriction (30, 31). Endotheliitis following virus internalization enhances endothelial injury, thrombogenesis, and immune recruitment, while the cytokine storm typical of severe cases may additionally boost the same mechanism in multiple anatomical districts (32). Moreover, sustained activation of the complement system causes microvascular injury and a procoagulant state triggered by the deposition of complement component C4d and colocalization of SARS-CoV-2 Spike protein in dermal vessels (33). All these mechanisms contribute to the inflammatory dermal microenvironment, which may be the subject of the innate and adaptive immune cell recruitment leading to the extension of inflammatory process toward the vessel wall, causing vasculitis. Another proposed pathogenetic mechanism may involve an autoimmune response targeting vessel wall components following a break of tolerance or molecular mimicry with SARS-CoV-2 proteins (34). Furthermore, CV was described in the context of Kawasaki-like syndrome, a generalized inflammatory disease affecting mainly infants for which the term "multisystem inflammatory syndrome in children (MIS-C) has been coined. However, the specificity of skin vasculitis in the setting of MIS-C still remains unclear, also due to the less frequency of skin biopsies performed in children.

All vaccines authorized for use by the U.S. *Food and Drug Administration* (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) have been thoroughly studied and found to be safe and effective in preventing severe COVID-19 cases (35). However, as globally millions of people have now been vaccinated, with increasing frequency, vaccination-related diseases have been observed (36), including CV.

Almost all the available COVID-19 vaccines have been associated with CV, e.g., mRNA vaccines (Pfizer BioNTech), mRNA-1273 (Moderna), adenoviral vector-based vaccines (ChAdOx1 nCoV-19; Oxford-AstraZeneca), and inactivated vaccines (Covaxin, Sinovac). Correlations between vaccination and the subsequent appearance of several types of vasculitis have been also described in the literature with vaccines against influenza, hepatitis B, serogroup B meningococcus, hepatitis A, Human Papilloma Virus (HPV) and with Bacillus of Calmette-Guérin (BCG) (37).

An important criterion guiding the assessment of causality is the temporal relationship between immunization and the side event: for drug- and vaccine-induced vasculitis it is considered to be in the range of 1–6 weeks (38). Most of the cases were self-limiting skin forms without systemic involvement, solved spontaneously or after systemic treatment.

The link between vasculitis and vaccination from a pathogenetic point of view is not clear but may involve an immune complex and antibodies deposition in the blood vessel walls (39). Recently, cytoplasmatic granular positivity for SARS-CoV-2 Spike protein was found in some skin specimens of infection-related CV (40). The vaccine proteins are structurally analogous to the wild viral antigens and could induce a pro-inflammatory cascade similar to that caused by the viral protein. Thus, vaccine antigens may activate B/T cells and cause antibody formation with subsequent immune complex deposition in small-caliber vessels. Along with this, Baiu et al. demonstrated the role of Th1 response and suggested that interferon-gamma is critically required for the initiation of vascular inflammation (41). Then, the whole-virion inactivated SARS-CoV-2 vaccine induces primarily a Th1-biased response, which could lead to the induction of an inflammatory response in the vessel wall (42). An open issue for patients who developed such adverse events following COVID-19 vaccination is whether the booster dose should be administered or not. In fact, repeating the administration could potentially cause more severe immunologic reactions (43). However, cutaneous small-vessel vasculitis secondary to infections, drugs, and vaccines is reported to have a less protracted course when compared to primary vasculitis. Therefore, this should not be a deterrent to the use of the COVID-19 vaccine, which is the most effective weapon to curb the pandemic (44).

Conclusion

Although rarely, CV has been reported in both SARS-CoV-2 -infected and SARS-CoV-2-vaccinated patients. In many cases, these were self-limiting skin forms without systemic involvement, solved spontaneously or after systemic treatment. Studies on this topic are however important to better understand the pathogenetic mechanisms underlying their origin.

With the evolution of the infection and with the finding of less aggressive SARS-CoV-2 variants, it will be necessary to follow the patients who will develop a CV, to better define their characteristics, and possibly understand which variants are more associated with the development of CV. Moreover, the epidemiological trend of COVID-19 infection and the need to protect especially the fragile population made it necessary to start a vaccination campaign with a fourth additional dose. Therefore, careful monitoring of these patients is essential to identify the presence of CV and to make a correct diagnosis, based not only on histological examination but also on DIF, essential to better define the characteristics of SARS-CoV-2 and vaccine-related CV.

Author contributions

AV, CHS, and MC contributed to conception and design of the study. EM organized the database of cases collected. AC, EM, VR, and AV wrote the first draft of the manuscript. LQ and CA wrote sections of the manuscript. All authors contributed to 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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References

1. Caproni M, Verdelli A. An update on the nomenclature for cutaneous vasculitis. *Curr Opin Rheumatol.* (2019) 31:46–52. doi: 10.1097/BOR.0000000000000563

2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* (2013) 65:1–11. doi: 10.1002/art.37715

3. Sunderkötter CH, Zelger B, Chen KR, Requena L, Piette W, Carlson JA, et al. Nomenclature of cutaneous vasculitis: dermatologic addendum to the 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheumatol.* (2018) 70:171–84. doi: 10.1002/art.40375

4. Filosa A, Verdelli A, Bianchi B, Del Bianco E, Bugatti L, Filosa G, et al. Cutaneous vasculitidis: histology and immunofluorescence. *G Ital Dermatol Venereol.* (2015) 150:183–91.

5. Morita TCAB, Criado PR, Criado RFJ, Trés GFS, Sotto MN. Update on vasculitis: overview and relevant dermatological aspects for the clinical and histopathological diagnosis - Part II. *An Bras Dermatol.* (2020) 95:493–507. doi: 10.1016/j.abd.2020.04.004

6. Morita TCAB, Trés GFS, Criado RFJ, Sotto MN, Criado PR. Update on vasculitis: an overview and dermatological clues for clinical and histopathological diagnosis - part I. *An Bras Dermatol.* (2020) 95:355–71. doi: 10.1016/j.abd.2020.01.003

7. Lath K, Chatterjee D, Saikia UN, Saikia B, Minz R, De D, et al. Role of direct immunofluorescence in cutaneous small-vessel vasculitis: experience from a tertiary center. *Am J*

Dermatopathol. (2018) 40:661–6. doi: 10.1097/DAD.0000000000001170

8. Nandeesh BN, Tirumalae R. Direct immunofluorescence in cutaneous vasculitis: experience from a referral hospital in India. *Indian J Dermatol.* (2013) 58:22–5. doi: 10.4103/0019-5154.105280

9. Micheletti RG, Werth VP. Small vessel vasculitis of the skin. *Rheum Dis Clin North Am.* (2015) 41:21–32. doi: 10.1016/j.rdc.2014.09.006

10. Antiga E, Verdelli A, Bonciani D, Bonciolini V, Quintarelli L, Volpi W, et al. Drug-induced cutaneous vasculitides. *G Ital Dermatol Venereol.* (2015) 150:203–10.

11. Gázquez Aguilera EM, Rodríguez García M, Cantón Yebra MT. Cutaneous vasculitis due to COVID-19 vaccination. *Med Clin.* (2022) 158:493–4. doi: 10.1016/j.medcle.2021.09.019

12. Valero C, Baldivieso-Achá JP, Uriarte M, Vicente-Rabaneda EF, Castañeda S, García-Vicuña R. Vasculitis flare after COVID-19: report of two cases in patients with preexistent controlled IgA vasculitis and review of the literature. *Rheumatol Int*. (2022) 42:5153. doi: 10.1007/s00296-022-05153-w

13. Criado PR, Giordani LP, Yoshimoto TA, Vieira IC, Landman G, Pincelli TP. Vasculitis in the setting of COVID-19: From the disease to the vaccine. report of a case of cutaneous vasculitis after immunization. *Dermatol Ther*. (2022) 35:15367. doi: 10.1111/dth.15367

14. Pendlebury GA, Oro P, Haynes W, Merideth D, Bartling S, Bongiorno MA. The impact of COVID-19 pandemic on dermatological conditions: a novel, comprehensive review. *Dermatopathology (Basel).* (2022) 9:212–43. doi: 10.3390/dermatopathology9030027

15. Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: a worldwide review. *JAAD Int.* (2021) 2:119–33. doi: 10.1016/j.jdin.2020.12.003

16. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, et al. Covid-19 and autoimmunity. *Autoimmun Rev*. (2020) 19:102597. doi: 10.1016/j.autrev.2020.102597

17. Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. *Autoimmun Rev*. (2021) 20:15651. doi: 10.1016/j.autrev.2021.102792

18. shakoei S, Kalantari Y, Nasimi M, Toutounchi NM, Ansari MS, Razavi Z, et al. Cutaneous manifestations following COVID-19 vaccination: a report of 25 cases. *Dermatol Ther*. (2022) 35:15651doi: 10.1111/dth.15651

19. Wollina U, Schönlebe J, Kodim A, Hansel G. Severe leukocytoclastic vasculitis after. covid-19 vaccination - cause or coincidence? Case report and literature review. *Georgian Med News [Internet].* (2022) 324:134–9.

20. WHO Coronavirus (COVID-19) Dashboard. *WHO Coronavirus (COVID-19) Dashboard With Vaccination Data*. (2022). Available online at: https://covid19.who.int/ (accessed July 20, 1985).

21. Luo X, Lv M, Zhang X, Estill J, Yang B, Lei R, et al. Clinical manifestations of COVID-19: an overview of 102 systematic reviews with evidence mapping. *J Evid Based Med*. (2022) 13:12. doi: 10.1111/jebm.12483

22. Purja S, Oh S, Kim E. A systematic review on neurological aspects of COVID-19: exploring the relationship between COVID-19-related olfactory dysfunction and neuroinvasion. *Front Neurol*. (2022) 13:164. doi: 10.3389/fneur.2022.887164

23. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou C, Quan H, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032

24. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol.* (2020) 34:e212–3. doi: 10.1111/jdv.16387

25. Farajzadeh S, Khalili M, Dehghani S, Babaie S, Fattah M, Abtahi-Naeini B. Top 10 acral skin manifestations associated with COVID-19: a scoping review. *Dermatol Ther*. (2021) 34:15157. doi: 10.1111/dth.15157

26. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: current knowledge and future perspectives. *Dermatology*. (2021) 237:1–12. doi: 10.1159/000512932

27. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol.* (2020) 183:71–7. doi: 10.1111/bjd.19163

28. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis.* (2020) 20:1135–40. doi: 10.1016/S1473-3099(20)30434-5

29. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty*. (2020) 9:62. doi: 10.1186/s40249-020-00662-x

30. Gencer S, Lacy M, Atzler D, Van Der Vorst EPC, Döring Y, Weber C. Immunoinflammatory, Thrombohaemostatic, and Cardiovascular Mechanisms in COVID-19. *Thromb Haemost.* (2020) 120:1629–41. doi: 10.1055/s-0040-1718735

31. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. (2005) 111:2605–10. doi: 10.1161/CIRCULATIONAHA.104.510461

32. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5

33. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. (2020) 220:1–13. doi: 10.1016/j.trsl.2020.04.007

34. Kaya G, Kaya A, Saurat JH. Clinical and histopathological features and potential pathological mechanisms of skin lesions in COVID-19: review of the literature. *Dermatopathology (Basel).* (2020) 7:3–16. doi: 10.3390/dermatopathology7010002

35. Shakoor MT, Birkenbach MP, Lynch M. ANCA-associated vasculitis following pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis.* (2021) 78:611–3. doi: 10.1053/j.ajkd.2021.06.016

36. Altun E, Kuzucular E. Leukocytoclastic vasculitis after COVID-19 vaccination. *Dermatol Ther*. (2022) 35:1527. doi: 10.1111/dth.15279

37. Carrillo-Garcia P, Sánchez-Osorio L, Gómez-Pavón J. Leukocytoclastic vasculitis in possible relation to the BNT162b2 mRNA COVID-19 vaccine. *J Am Geriatr Soc.* (2022) 70:971–3. doi: 10.1111/jgs.17675

38. Colia R, Rotondo C, Corrado A, Cantatore FP. Cutaneous vasculitis after severe acute respiratory syndrome coronavirus 2 vaccine. *Rheumatol Adv Pract*. (2021) 5:50. doi: 10.1093/rap/rkab050

39. Azzazi Y, Abdelkader HA, Khedr H, El-Komy MHM. Extensive cutaneous leukocytoclastic vasculitis after Sinopharm vaccine: Case report and review of the literature. *J Cutan Pathol.* (2022) 49:14235. doi: 10.1111/cup.14235

40. Santonja C, Heras F, Núñez L, Requena L. COVID-19 chilblain-like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative patient. *Br J Dermatol.* (2020) 183:778–80. doi: 10.1111/bjd.19338

41. Baiu DC, Sandor M, Hart M. CD4+ T cells sensitized by vascular smooth muscle induce vasculitis, and interferon gamma is critical for the initiation of vascular pathology. *Am J Pathol.* (2010) 177:3215–23. doi: 10.2353/ajpath.2010.090985

42. Dash S, Behera B, Sethy M, Mishra J, Garg S. COVID-19 vaccine-induced urticarial vasculitis. *Dermatol Ther*. (2021) 34:15093. doi: 10.1111/dth.15093

43. Sirufo MM, Raggiunti M, Magnanimi LM, Ginaldi L, De Martinis M. Henoch-Schönlein Purpura Following the first dose of cOVID-19 viral vector vaccine: a case report. *Vaccines (Basel).* (2021) 9:1078. doi: 10.3390/vaccines9101078

44. Kar BR, Singh BSTP, Mohapatra L, Agrawal I. Cutaneous small-vessel vasculitis following COVID-19 vaccine. *J Cosmet Dermatol.* (2021) 20:3382–3. doi: 10.1111/jocd.14452

45. Capoferri G, Daikeler T, Mühleisen B, Trendelenburg M, Müller S. Cutaneous leukocytoclastic vasculitis secondary to COVID-19 infection leading to extensive skin necrosis. *Clin Dermatol*. (2022). doi: 10.1016/j.clindermatol.2022.02.013. [Epub ahead of print].

46. Yildirim Bay E, Moustafa E, Semiz Y, Gündogdu O, Oguz Topal I, Yalçin Ö. Leukocytoclastic vasculitis secondary to COVID-19 infection presenting with inclusion bodies: a histopathological correlation. *J Cosmet Dermatol.* (2022) 21:27–9. doi: 10.1111/jocd.14637

47. Gosnell HL, Grider DJ. Urticarial vasculitis: a potential signpost for multisystem inflammatory syndrome in children. *J Cutan Pathol.* (2022) 49:163–6. doi: 10.1111/cup.14134

48. Kumar G, Pillai S, Norwick P, Bukulmez H. Leucocytoclastic vasculitis secondary to COVID-19 infection in a young child. *BMJ Case Rep*. (2021) 14:1–4. doi: 10.1136/bcr-2021-242192

49. Nassani N, Sweiss N, Berry JT, Calhoun C, Polick A, Trivedi I. Leukocytoclastic Vasculitis in Cutaneous Crohn Disease in the Setting of COVID-19. *Inflamm Bowel Dis.* (2021) 27:E74–5. doi: 10.1093/ibd/izab045

50. Iraji F., Galehdari H, Siadat AH, Bokaei Jazi S. Cutaneous leukocytoclastic vasculitis secondary to COVID-19 infection: a case report. (2021) 9:830–4. doi: 10.1002/ccr3.3596

51. Jedlowski PM, Jedlowski MF. Coronavirus disease 2019-associated immunoglobulin A vasculitis/Henoch–Schönlein purpura: a case report and review. *J Dermatol.* (2022) 49:190–6. doi: 10.1111/1346-8138.16211

52. Gouveia PA da C, Cipriano IC, de Melo MAZ, da Silva HTA, Amorim MA de O, de Sá Leitão CC, et al. Exuberant bullous vasculitis associated with SARS-CoV-2 infection. *IDCases*. (2021) 23:e01047. doi: 10.1016/j.idcr.2021.e01047

53. Kösters K, Schwarzer S, Labuhn A, Rübben A, Yang S, Hessler F, et al. Cutaneous vasculitis in a patient with COVID-19. *Open Forum Infect Dis*. (2020) 7:474. doi: 10.1093/ofid/ofaa474

54. Gómez MC, González-Cruz C, Ferrer B, Barberá MJ. Leucocytoclastic vasculitis in a patient with COVID-19 with positive SARS-CoV-2 PCR in skin biopsy. *BMJ Case Rep*. (2020) 13:238039. doi: 10.1136/bcr-2020-238039

55. Skroza N, Bernardini N, Balduzzi V, Mambrin A, Marchesiello A, Michelini S, et al. A late-onset widespread skin rash in a previous COVID-19-infected patient: viral or multidrug effect? *J Eur Acad Dermatol Venereol.* (2020) 34:e438–9. doi: 10.1111/jdv.16633

56. Nasiri S, Dadkhahfar S, Abasifar H, Mortazavi N, Gheisari M. Urticarial vasculitis in a COVID-19 recovered patient. *Int J Dermatol.* (2020) 59:1285–6. doi: 10.1111/ijd.15112

57. Caputo V, Schroeder J, Rongioletti F, A. generalized purpuric eruption with histopathologic features of leucocytoclastic vasculitis in a patient severely ill with COVID-19. *J Eur Acad Dermatol Venereol.* (2020) 34:e579–81. doi: 10.1111/jdv.16737

58. de Perosanz-Lobo D, Fernandez-Nieto D, Burgos-Blasco P, Selda-Enriquez G, Carretero I, Moreno C, et al. Urticarial vasculitis in COVID-19 infection: a vasculopathy-related symptom? *J Eur Acad Dermatol Venereol.* (2020) 34:e566–8. doi: 10.1111/jdv.16713

59. Dominguez-Santas M, Diaz-Guimaraens B, Garcia Abellas P, Moreno-Garcia del Real C, Burgos-Blasco P, Suarez-Valle A. Cutaneous small-vessel vasculitis associated with novel 2019 coronavirus SARS-CoV-2 infection (COVID-19). *J Eur Acad Dermatol Venereol*. (2020) 34:e536–7. doi: 10.1111/jdv.16663

60. Mayor-Ibarguren A, Feito-Rodriguez M, Quintana Castanedo L, Ruiz-Bravo E, Montero Vega D, Herranz-Pinto P. Cutaneous small vessel vasculitis secondary to COVID-19 infection: a case report. *J Eur Acad Dermatol Venereol.* (2020) 34:e541–2. doi: 10.1111/jdv.16670

61. Li NL, Papini AB, Shao T, Girard L. Immunoglobulin-A vasculitis with renal involvement in a patient with COVID-19: a case report and review of acute kidney injury related to SARS-CoV-2. *Can J Kidney Health Dis*. (2021) 8:1684. doi: 10.1177/2054358121991684

62. Sandhu S, Chand S, Bhatnagar A, Dabas R, Bhat S, Kumar H, et al. *Possible Association Between IgA Vasculitis and COVID-19. Dermatol Ther*. (2021) 34:e14551. doi: 10.1111/dth.14551

63. Đordević Betetto L, Luzar B, Pipan Tkalec Ž, Ponorac S. Cutaneous leukocytoclastic vasculitis following COVID-19 vaccination with Ad26.COV2.S vaccine: a case report and literature review. Acta Dermatovenerologica Alpina Pannonica et Adriatica. (2022) 31:83–7. doi: 10.15570/actaapa.2022.12

64. Fiorillo G, Pancetti S, Cortese A, Toso F, Manara S, Costanzo A, et al. Leukocytoclastic vasculitis (cutaneous small-vessel vasculitis) after COVID-19 vaccination. *J Autoimmun*. (2022) 127:102783. doi: 10.1016/j.jaut.2021.102783

65. Vornicu A, Berechet A, Frăʔilă G, Obrişcă B, Jurcut C, Ismail G. Relapse of cryoglobulinemic vasculitis with new-onset severe renal involvement in two patients following mRNA COVID-19 vaccination: a case report. *Medicine [Internet]*. (2022) 101:e29431. doi: 10.1097/MD.0000000000029431

66. Sandhu S, Bhatnagar A, Kumar H, Dixit PK, Paliwal G, Suhag DK, et al. Leukocytoclastic vasculitis as a cutaneous manifestation of ChAdOx1 nCoV-19 corona virus vaccine (recombinant). *Dermatol Ther*. (2021) 34:15142. doi: 10.1111/dth.15141

67. Cohen SR, Prussick L, Kahn JS, Gao DX, Radfar A, Rosmarin D. Leukocytoclastic vasculitis flare following the COVID-19 vaccine. *Int J Dermatol [Internet]*. (2021) 60:1032–3. doi: 10.1111/ijd.15623

68. Larson V, Seidenberg R, Caplan A, Brinster NK, Meehan SA, Kim RH. Clinical and histopathological spectrum of delayed adverse cutaneous reactions following COVID-19 vaccination. *J Cutan Pathol [Internet]*. (2022) 49:34–41. doi: 10.1111/cup.14104

69. Bostan E, Zaid F, Akdogan N, Gokoz O. Possible case of mRNA COVID-19 vaccine-induced small-vessel vasculitis. *J Cosmet Dermatol [Internet]*. (2022) 21:51–3. doi: 10.1111/jocd.14568

70. Gambichler T, Abu Rached N, Scholl L, Behle B, Mansour R, Nick M, et al. Reproducible leukocytoclastic vasculitis following severe acute respiratory syndrome coronavirus 2 vaccination. *J Dermatol [Internet]*. (2022) 49:145–6. doi: 10.1111/1346-8138.16282

71. Ireifej B, Weingarten M, Dhamrah U, Weingarten M, Hadi S. Leukocytoclastic Vasculitic Rash Following Second Dose of Moderna COVID-19 Vaccine. *J Investig Med High Impact Case Rep*. (2022) 10:6283. doi: 10.1177/23247096211066283

72. Grossman ME, Appel G, Little AJ, Ko CJ. Post-COVID-19 vaccination IgA vasculitis in an adult. *J Cutan Pathol [Internet]*. (2022) 49:385–7. doi: 10.1111/cup.14168

73. Mücke VT, Knop V, Mücke MM, Ochsendorf F, Zeuzem S. First description of immune complex vasculitis after COVID-19 vaccination with BNT162b2: a case report. *BMC Infect Dis*. (2021) 21:958. doi: 10.1186/s12879-021-06655-x

74. Dicks AB, Gray BH. Images in vascular medicine: leukocytoclastic vasculitis after COVID-19 vaccine booster. *Vasc Med [Internet]*. (2022) 27:100–1. doi: 10.1177/1358863X211055507

75. Mohamed MMB, Wickman TJ, Fogo AB, Velez JCQ, De. Novo immunoglobulin a vasculitis following exposure to SARS-CoV-2 immunization. *Ochsner J [Internet]*. (2021) 21:395–401. doi: 10.31486/toj.21.0083

76. Hines AM, Murphy N, Mullin C, Barillas J, Barrientos JC. Henoch-Schönlein purpura presenting post COVID-19 vaccination. *Vaccine [Internet]*. (2021) 39:4571–2. doi: 10.1016/j.vaccine.2021.06.079

77. Cavalli G, Colafrancesco S, de Luca G, Rizzo N, Priori R, Conti F, et al. Cutaneous vasculitis following COVID-19 vaccination. *Lancet Rheumatol.* (2021) 3:e743–4. doi: 10.1016/S2665-9913(21)00309-X

78. Guzmán-Pérez L, Puerta-Peña M, Falkenhain-López D, Montero-Menárguez J, Gutiérrez-Collar C, Rodríguez-Peralto JL, et al. Small-vessel vasculitis following Oxford-AstraZeneca vaccination against SARS-CoV-2. *J Eur Acad Dermatol Venereol.* (2021) 35:e741–3. doi: 10.1111/jdv.17547

79. Shahrigharahkoshan S, Gagnon LP, Mathieu S. Cutaneous leukocytoclastic vasculitis induction following ChAdOx1 nCoV-19 vaccine. *Cureus*. (2021) 13:19005. doi: 10.7759/cureus.19005

80. Jin WJ, Ahn SW, Jang SH, Hong SM, Seol JE, Kim H. Leukocytoclastic vasculitis after coronavirus disease 2019 vaccination. *J Dermatol.* (2022) 49:e34–5. doi: 10.1111/1346-8138.16212

81. Fritzen M, Funchal GDG, Luiz MO, Durigon GS. Leukocytoclastic vasculitis after exposure to COVID-19 vaccine. *An Bras Dermatol.* (2022) 97:118–21. doi: 10.1016/j.abd.2021.09.003

82. Kharkar V, Vishwanath T, Mahajan S, Joshi R, Gole P. Asymmetrical cutaneous vasculitis following COVID-19 vaccination with unusual eosinophil preponderance. *Clin Exp Dermatol.* (2021) 46:1596–7. doi: 10.1111/ced.14797

83. Oskay T, Isik M. Leukocytoclastic vasculitis after the third dose of CoronaVac vaccination. *Clin Rheumatol.* (2022) 41:1931–3. doi: 10.1007/s10067-021-05993-0

84. Bostan E, Gulseren D, Gokoz O. New-onset leukocytoclastic vasculitis after COVID-19 vaccine. *Int J Dermatol.* (2021) 60:1305–6. doi: 10.1111/ijd.15777

85. Erler A, Fiedler J, Koch A, Heldmann F, Schütz A. Leukocytoclastic vasculitis after vaccination with a SARS-CoV-2 vaccine. *Arthritis Rheumatol [Internet]*. (2021) 73:2188. doi: 10.1002/art.41910

86. Bencharattanaphakhi R, Rerknimitr P. Sinovac COVID-19 vaccine-induced cutaneous leukocytoclastic vasculitis. *JAAD Case Rep*. (2021) 18:1–3. doi: 10.1016/j.jdcr.2021.10.002