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# A case report navigating CVID and sarcoidosis overlaps in pediatric nephritis

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Common variable immunodeficiency (CVID) can be complicated by granulomatous disease, often granulomatous lymphocytic interstitial lung disease (GLILD). Granulomatous interstitial nephritis represents an atypical presentation in pediatrics. Our patient is a previously healthy 13-year-old white male with a recent diagnosis of CVID. He presented with a rash and laboratory findings included pancytopenia (white blood cells  $2.6 \times 10^3/\mu\text{l}$ , hemoglobin 11.8 g/dl, platelets  $60 \times 10^3/\mu\text{l}$ ), hypercalcemia (14.9 mg/dl), elevated Vit D  $1,25 \text{ OH level } (>200 \text{ pg/ml})$ , hyperuricemia (8.8 mg/dl), and acute kidney injury (AKI) (serum creatinine 1.1 mg/dl; baseline 0.64 mg/dl). A broad infectious workup was unremarkable. The rash improved with empiric doxycycline. Hypercalcemia and hyperuricemia were managed with fluid resuscitation, calcitonin, and zoledronic acid. Evaluation for malignancy including a positron emission tomography scan, revealed multiple mediastinal hypermetabolic lymph nodes and pulmonary ground glass opacities, later reported as small pulmonary nodules by computed tomography (CT). Splenomegaly was confirmed by ultrasound and CT. Peripheral smear, bone marrow biopsy, and genetic testing were non-revealing. His angiotensin-converting enzyme level was elevated (359 U/L), raising concerns for sarcoidosis. Given Stage 1 AKI, a renal biopsy was pursued and identified non-caseating granulomatous interstitial nephritis. Treatment with 60 mg of prednisone began for presumed sarcoidosis for 4 months, causing steroid-induced hypertension and mood changes. Zoledronic acid minimally reduced serum creatinine. *Pneumocystis jirovecii* pneumonia prophylaxis was initiated due to T-cell cytopenia. Chest CT findings showed a suboptimal response to steroids. A bronchoalveolar lavage demonstrated  $>50\%$  lymphocytes (normal  $<10\%$ ) and the lung biopsy exhibited non-caseating granulomas, indicating GLILD. Rubella was identified by staining. Following a fever, he was found to have elevated liver enzymes and confirmed hepatitis with portal hypertension on CT. A liver biopsy revealed epithelioid non-caseating granuloma and HHV6 was detected by PCR. He was treated with four cycles of rituximab and granulocyte-colony stimulating factor for persistent neutropenia. Subsequent treatment with mycophenolate led to the resolution of the granulomatous lesions and cytopenias. The rare complication of granulomatous interstitial nephritis in CVID illustrates the intricate nature of diagnosis. This case

underscores the necessity for a holistic view of the patient's clinical and immune phenotype, including distinctive radiological presentations, for precise diagnoses and tailored management of CVID.

#### KEYWORDS

CVID, granulomatous disease, hypogammaglobulinemia, sarcoidosis, GLILD, granulomatous lymphocytic interstitial lung disease

## Introduction

Common variable immunodeficiency (CVID) is among the most commonly diagnosed primary immunodeficiencies (1–3). The term “variable” reflects the heterogeneous clinical presentations of patients who present with hypogammaglobulinemia and increased susceptibility to infections. The vast majority of patients lack an identifiable underlying molecular defect (4). Granulomatous disease occurs in 8%–22% of CVID patients, often affecting the lungs, lymph nodes, and spleen (5–10). Granulomatous lesions appear on organ biopsies and may precede recognition of any underlying immune defects (6–11). Resultantly, a diagnosis of CVID is often delayed and occasionally patients might be mislabeled as having sarcoidosis due to clinical overlap and the greater prevalence of sarcoidosis (5, 12). These diagnostic delays can be significantly associated with increased morbidity and mortality contributions in CVID (13). The clinical impact of non-infectious manifestations, such as granulomas, is organ-specific, and the presence of granulomas and subsequent tissue damage in the lungs and liver have been demonstrated to lead to shorter patient survival (14).

Lymphocytic interstitial infiltrate, accompanying granuloma formation, contributes to organ failure and disease severity, as seen in “granulomatous lymphocytic interstitial lung disease” or GLILD (5, 9, 15). Granuloma presence, alongside autoimmune manifestations in CVID, can significantly elevate mortality risk, particularly in pediatric-onset cases (8, 13). The development of granulomas and autoimmunity in CVID each independently pose therapeutic challenges, necessitating a careful balance of immunosuppression in an already compromised immune system. Granulomatous interstitial nephritis in adult patients with CVID has been very sparsely reported in the literature (16–18). We aim to describe a unique and rare presentation of granulomatous interstitial nephritis in a pediatric patient with known CVID. We highlight the diagnostic challenge of distinguishing CVID-associated granulomatous disease from sarcoidosis and describe the management and clinical progression of our patient, in accordance with CARE Guidelines (19).

## Narrative

Our patient was a previously healthy 13-year-old white male referred to the Allergy and Immunology service by his pediatrician following hypogammaglobulinemia identified on screening for celiac disease due to a known family history. Family history was remarkable for ulcerative colitis in the mother

and an older brother with celiac disease. The patient lacked a history of recurrent or unusual infections. Immune phenotyping at the time of diagnosis (Table 1) included a complete blood count with pancytopenia [white blood cell (WBC) count  $3.08 \times 10^3/\mu\text{l}$ , hemoglobin 12.5 g/dl, platelets  $71 \times 10^3/\mu\text{l}$ ]. He was also noted to have decreased lymphocyte subsets upon initial evaluation: CD3+ T-cell count  $584 \times 10^3/\mu\text{l}$ , CD3+CD4+ T-cell count  $309 \times 10^3/\mu\text{l}$ , CD3+CD8+ T-cell count  $215 \times 10^3/\mu\text{l}$ , CD19+ B-cell count  $100 \times 10^3/\mu\text{l}$ , and CD3–CD56+CD16+ NK cell count  $27 \times 10^3/\mu\text{l}$ . The B-cell subset had absent class-switched memory B cells, CD19<sup>+</sup>CD27<sup>+</sup>IgM<sup>−</sup>IgD<sup>−</sup> at 0%, and elevated transitional B-cell percentage, CD19+CD38+Bright IgM at 17% with a normal count of  $16 \times 10^3/\mu\text{l}$  identified. CD19+CD38<sup>−/low</sup>, CD21<sup>−/low</sup> autoreactive B cells were found to be  $1 \times 10^3/\mu\text{l}$ . He had diffuse hypogammaglobulinemia with IgG 246 mg/dl, IgA 18 mg/dl, and IgM 7 mg/dl. Pneumococcal IgG antibodies were positive in only 1 out of 23 serotypes, with a level  $>1.3 \mu\text{g/ml}$ . The patient was up to date on his childhood vaccines.

Shortly after the initial immune evaluation, our patient developed a diffuse non-blanching maculopapular rash and progression of pancytopenia (WBC  $2.66 \times 10^3/\mu\text{l}$ , Hemoglobin 11.8 g/dl, Platelet  $60 \times 10^3/\mu\text{l}$ ) following a camping trip in the Ozarks, an area endemic for several tick-borne illnesses, which occurred 1 month before the rash onset. His rash was non-pruritic, noted to involve the palms and soles, and appeared petechial in nature around his thighs and axilla. Screening labs on admission displayed hypercalcemia (14.9 mg/dl), elevated Vitamin D 1,25 OH level ( $>200 \text{ pg/ml}$ ), hyperuricemia (8.8 mg/dl), and acute kidney injury (AKI) (serum creatinine 1.1 mg/dl up from baseline 0.64 mg/dl). Soluble IL-2 was elevated to a peak of 8,711 U/ml, with ratio of soluble IL-2 to WBC of 3.5.

The constellation of pancytopenia, hypercalcemia, and hyperuricemia triggered an evaluation for malignancy. The positron emission tomography (PET) (Figure 1a) scan showed multiple hypermetabolic lymph nodes within his mediastinum nodal enlargement and pulmonary ground glass opacities. Computed tomography (CT) (Figure 1b) later reported pulmonary changes as diffuse small pulmonary nodules. Splenomegaly was confirmed by ultrasound (US) and CT, and left kidney enlargement was seen on the US. Peripheral smear and bone marrow biopsy findings were normal. Concurrent broad evaluation for infection, including tick-borne illnesses, was pursued and was unremarkable. A critical trio whole-exome sequencing was also unrevealing. He was started on a 10-day empiric course of doxycycline with an improvement in the rash. Hypercalcemia and hyperuricemia were managed with fluid

TABLE 1 Laboratory studies at diagnosis.

Complete blood count	Patient's value	Normal value
White blood cell count	<b>3.08 × 10<sup>3</sup>/μl</b>	4.5–13.5 × 10 <sup>3</sup> /μl
Hemoglobin	<b>12.5 g/dl</b>	13.0–16.0 g/dl
Platelets	<b>71 × 10<sup>3</sup>/μl</b>	150–450 × 10 <sup>3</sup> μl
<b>Immunophenotyping</b>		
CD3 <sup>+</sup> cells × 10 <sup>3</sup> /ml (%)	<b>584 × 10<sup>3</sup>/μl (82)</b>	1,000–2,200 × 10 <sup>3</sup> /μl (60–76)
CD4 <sup>+</sup> T cells × 10 <sup>3</sup> /ml (%)	<b>309 × 10<sup>3</sup>/μl (43)</b>	530–1,300 × 10 <sup>3</sup> /μl (31–52)
CD8 <sup>+</sup> T cells × 10 <sup>3</sup> /ml (%)	<b>215 × 10<sup>3</sup>/μl (30)</b>	330–920 × 10 <sup>3</sup> (18–35)
CD4 <sup>+</sup> /CD8 <sup>+</sup> T-cell ratio	1.44	0.7–2.4
CD19 <sup>+</sup> B cells × 10 <sup>3</sup> /ml (%)	<b>100 × 10<sup>3</sup>/μl (14)</b>	110–570 × 10 <sup>3</sup> /μl (6–23)
CD27 <sup>+</sup> Memory B cells × 10 <sup>3</sup> /ml (%)	3 × 10 <sup>3</sup> /μl (4)	2–122 × 10 <sup>3</sup> /μl (2–36)
CD19 <sup>+</sup> CD27 <sup>+</sup> IgM <sup>-</sup> IgD <sup>-</sup> Class-Switched Memory B cells × 10 <sup>3</sup> /ml (%)	0 × 10 <sup>3</sup> /μl (0)	0–74 × 10 <sup>3</sup> /μl (0–22)
CD19 <sup>+</sup> CD38 <sup>+</sup> Bright IgM <sup>+</sup> Transitional B cells × 10 <sup>3</sup> /ml (%)	16 × 10 <sup>3</sup> /μl (17)	0–18 × 10 <sup>3</sup> /μl (0–6)
CD56 <sup>+</sup> CD16 <sup>+</sup> NK cells × 10 <sup>3</sup> /ml (%)	<b>27 × 10<sup>3</sup>/μl (4)</b>	70–480 × 10 <sup>3</sup> /μl (3–22)
CD19 <sup>+</sup> CD38 <sup>-/low</sup> CD21 <sup>-/low</sup> autoreactive B cells	1 × 10 <sup>3</sup> (1)	0–21 × 10 <sup>3</sup> /μl (0%–7%)
<b>Mitogenic and antigenic induced lymphocyte proliferation</b>		
Phytohemagglutinin 10 μg/ml	<b>40, 826 lymphocyte proliferation in counts per minute</b>	>163,507 Lymphocyte proliferation in counts per minute
Tetanus antigen	4,340 Lymphocyte proliferation in counts per minute	>2,000 lymphocyte proliferation in counts per minute
<b>Cytokines</b>		
Soluble IL-2 receptor (CD25)	<b>8,711 U/ml</b>	45–1,105 unit/ml
<b>Immunoglobulins</b>		
IgG	246 mg/dl	641–1,353 mg/dl
IgA	18 mg/dl	66–295 mg/dl
IgM	7 mg/dl	40–80 mg/dl
<b>Vaccination antigen response</b>		
Pneumococcal IgG	1/23 > 1.3 μg/dl	50%–70% > 1.3 μg/dl
<i>Haemophilus influenzae</i> B IgG	<0.15 μg/ml	≥1.00 μg/ml
Tetanus antitoxoid	0.10 IU/ml	≥0.10 IU/ml

Bold values represent those values outside of the listed reference ranges.

resuscitation, calcitonin, and zoledronic acid. He received intravenous IgG replacement (500 mg/kg) during admission and continued monthly replacement with a goal trough of 1,000 mg/ml.

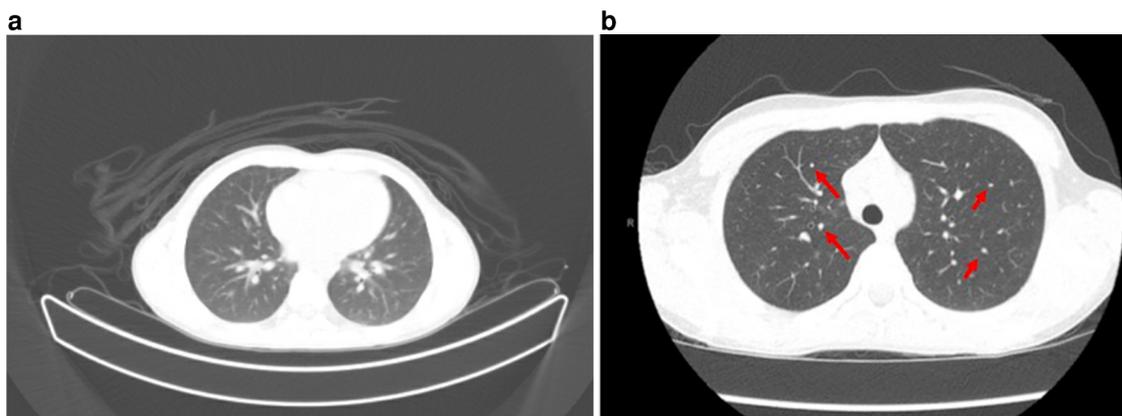
The presence of hypercalcemia, elevated Vitamin D levels, hypermetabolic lymph nodes, and pulmonary manifestations prompted an assessment for lymphoproliferative disorder. A renal biopsy was obtained due to Stage 1 AKI and identified non-caseating granuloma on electron microscopy, raising concern for sarcoidosis. Hematoxylin and eosin staining revealed numerous well-formed epithelioid, non-caseating granulomas with focal extension into renal tubules, in addition to the presence of focal calcified bodies and Langerhans-type giant cells. His angiotensin-converting enzyme (ACE) level was found to be elevated at 359 U/L (reference range 13–100 U/L), and universal polymerase chain reaction (PCR) testing on the renal biopsy was found to be negative for acid-fast bacilli, bacterial, and fungal infection.

A course of prednisone 60 mg daily for presumed sarcoidosis was initiated for a 4-month period with a slow taper. While on steroids, he developed side effects including steroid-induced hypertension and mood changes, in addition to a suboptimal clinical response. He also remained cytopenic while on steroid therapy and required *Pneumocystis jirovecii* pneumonia prophylaxis for persistent T-cell lymphopenia. Chest CT findings also showed an almost negligible response to steroids; though some nodules were resolving, there

was formation of new nodules (Figure 2). A bronchoalveolar lavage had greater than 50% lymphocytes (normal <10%). A lung biopsy was pursued to further characterize the lung nodules identified on CT to dictate the next therapeutic steps and it confirmed the presence of multi-organ granulomatous disease with the presence of non-caseating granulomas and lymphocytic inflammation, suggesting a diagnosis of GLILD.

Shortly after the biopsy, he spiked a fever and was found to have elevated liver enzymes. CT and ultrasound findings confirmed hepatitis with a suspicion of portal hypertension. A liver biopsy was performed and revealed epithelioid granulomas without necrotizing or caseating features, with the presence of focal areas of lobular and portal chronic inflammation. Histochemical staining identified focal glycogenated nuclei without copper or iron accumulation. Human herpes virus (HHV6) was detected in liver tissue by PCR.

He was treated with four cycles of rituximab, which normalized hemoglobin and platelet counts; however, he remained persistently neutropenic. Resultantly, he was started on granulocyte-colony stimulating factor (G-CSF) 5 μg/kg/day, which led to an improvement in absolute neutrophil counts. He subsequently received treatment with mycophenolate (MMF) for immune-mediated cytopenias, in addition to his multi-organ granulomatous disease, with good response, allowing discontinuation of G-CSF.



**FIGURE 1**  
 (a) PET scan with multiple mediastinal, axillary, and common hilar lymph nodes are appreciated, with representative lymph nodes. Multiple ground glass nodules within the bilateral lungs predominantly in a centrilobular distribution. Additional indistinct ground glass opacities along the posterior aspect of the bilateral lung. (b) CT scan with enlarged mediastinal lymph nodes demonstrated, correlating with hypermetabolic nodes from PET above. Multiple non-specific subcentimeter ground glass nodules (red arrows) throughout both lungs.

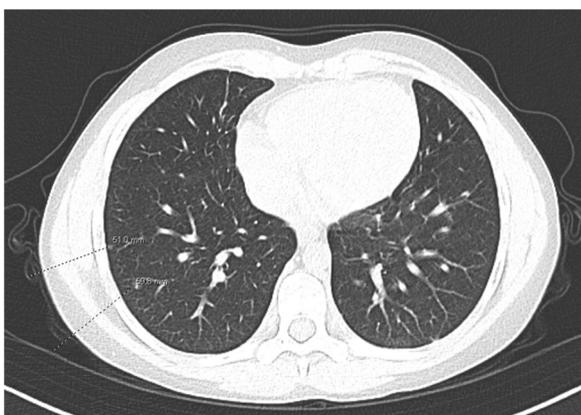
Due to a lack of steroids and the patient’s intolerance to side effects, no further steroids were administered. Our patient demonstrated improvements in white blood cell, hemoglobin, and platelet counts. While he remained T-cell lymphopenic, he maintained normal lymphocyte proliferation, obviating the need for *Pneumocystis jirovecii* prophylaxis. Following 2 years of therapy, he experienced complete resolution of pulmonary ground glass opacities and nodules, and hepatosplenomegaly.

## Discussion

Granulomatous findings in the tissue of patients with CVID have been noted to be mistaken for sarcoidosis (7, 12). Discriminating between these conditions can be complex due to overlapping

clinical and diagnostic features, including multi-system non-caseating granulomas with hypercalcemia, lymphadenopathy, and propensity for pulmonary, liver, and lymph node involvement (20, 21). In some situations, arriving at an accurate diagnosis can be further complicated by an immune phenotype not yet identified.

Elucidating the differences between granulomatous disease in CVID and sarcoidosis is critically important to avoid inappropriate treatment and delays in targeted treatment (Table 2). Many patients with sarcoidosis in fact have normal ACE levels (7, 22, 23). ACE levels have also been reported to be abnormally elevated in CVID patients without granulomas (8). Further, ACE levels can be elevated in the setting of certain infections such as the human immunodeficiency virus (HIV) and other infections presenting with non-caseating granulomas such as histoplasmosis (24, 25). Both sarcoidosis and granulomatous disease in CVID include B-cell derangements; however, CVID can be delineated by the absence or the reduction of switched memory B cells, and



**FIGURE 2**  
 CT following the use of steroids. Mixed response in multiple pulmonary nodules, with some nodules having resolved and other nodules new.

**TABLE 2** Key comparisons in CVID with GLILD and sarcoidosis.

Feature	CVID with GLILD	Sarcoidosis
B-cell subset	Absent or reduced memory switched B cells	Reduced memory B cells
Immunoglobulins	Hypogammaglobulinemia	Hypergammaglobulinemia or normal
Lung granulomas	Present	Present
Lymph node biopsy histologic findings	Ill-defined germinal centers, decreased plasma cells	Undisrupted architecture
Chest CT findings	Lower lung lobe with larger nodularity, ground glass opacities, and flame-shaped hemorrhages	Perilymphatic micronodular infiltrate in bronchovascular distribution
Bronchoalveolar lavage fluid	Normal CD4:CD8 (<3:1)	Elevated CD4:CD8 ratio (>3:5)
ACE levels	Normal or elevated	Normal or elevated
Spontaneous remission	Rare	Common in early stages

sarcoidosis favors reduced memory B cells alone (20). Sarcoidosis is typically characterized by the presence of hypergammaglobulinemia rather than hypogammaglobulinemia, a hallmark of CVID (26). Notably, patients with CVID and GLILD display markers reflecting T-cell activation and exhaustion, including soluble IL-2 receptor when compared to other patients with CVID with non-infectious complications (27).

From a histopathologic standpoint, lymphoid hyperplasia has been observed alongside granulomas in CVID and is absent in sarcoidosis. Specifically, patients with GLILD have exhibited CD4+ T-cell predominance in the lungs, variable CD8+ T cells and B cells were found in much smaller numbers. A notable absence of regulatory T cells in lung biopsies has also been reported (28). Follicular helper T cells have been noted within granuloma in CVID, whereas they are more weakly expressed in sarcoidosis (29). The presence of organizing pneumonias has been found in GLILD and a subgroup of patients with CVID and GLILD will progress to interstitial fibrosis with architectural remodeling (28).

Lymph node biopsy in CVID patients usually demonstrates disrupted architecture with ill-defined germinal centers and marked reductions in plasma cells, whereas plasma cells and germinal cells are more likely to be intact in sarcoidosis (20, 30). High-resolution CT and bronchoalveolar lavage findings can also help discriminate these conditions (12). GLILD on chest CT is more likely to include lower lobe disease with larger nodularity, ground glass opacities, and flame-shaped hemorrhages, while sarcoidosis is more often associated with perilymphatic micronodular infiltrate appearing in a bronchovascular distribution (31, 32). In the bronchoalveolar fluid, a CD4:CD8 ratio is typically normal in CVID and elevated (>3.5) in sarcoidosis (32).

It is estimated that 2% of patients with CVID have renal insufficiency (33). One study indicated that membranous glomerulonephropathy and tubulointerstitial nephritis were the predominant pathologic findings in renal biopsies from CVID patients with AKI and/or proteinuria (34).

Interstitial lymphocytic infiltration, in conjunction with granulomatous formations, indicates an increased risk of organ failure and disease severity (5). While up to 22% of patients with CVID have some variation of granulomatous disease, this prevalence is likely under-representative as most patients do not undergo routine biopsies (2, 35, 36). Tissue biopsy is not only crucial for diagnosis of granulomas but also to distinguish it from other conditions such as lymphoid hyperplasia and lymphomas (37, 38).

Our patient developed an exceedingly rare complication of granulomatous interstitial nephritis in CVID, in addition to GLILD, liver granulomas, and cytopenias. Initially, a diagnosis of sarcoidosis was made, however, his clinical presentation and features were more consistent with the granulomatous manifestations known to occur in CVID. An elevated soluble IL-2 receptor to white blood cell ratio, as was present in our patient, has been demonstrated to reflect granulomatous disease progression in CVID and may represent an important and readily available biomarker for risk stratification for this disease population (39). He clinically responded to a tailored treatment regimen with four cycles of rituximab, G-CSF, and mycophenolate for persistent neutropenia with resolution of the granulomas (Figure 3) and cytopenias.

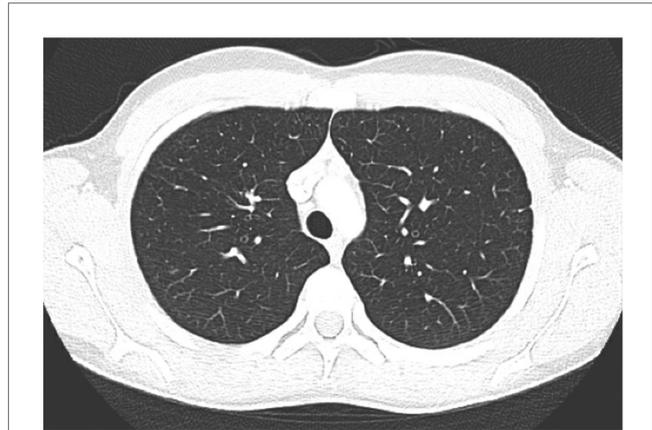


FIGURE 3

CT scan demonstrating interval near resolution of previously described punctate nodules throughout both lungs. Two isolated ground glass foci remain with the right lung. No new nodule or ground glass opacity.

## Conclusion

This case underscores the diagnostic complexities inherent in differentiating CVID-related granulomatous disease from other similar conditions. The coexistence of hypogammaglobulinemia with specific chest CT findings steered the diagnosis toward GLILD rather than sarcoidosis. This case emphasizes the necessity of a thorough evaluation of a patient's clinical presentation and immune phenotyping when CVID-related granulomatous anomalies are suspected. Meticulous attention to the distinctive clinical and diagnostic features is paramount for achieving an accurate diagnosis, which is crucial for the effective management and targeted treatment of patients with CVID.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to amanda.salih@alumni.bcm.edu.

## Ethics statement

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

AS: Writing – review & editing, Writing – original draft. AB: Writing – review & editing. AG: Writing – review & editing. SH: Writing – review & editing. MS-C: Writing – review & editing.

LT: Writing – review & editing. JH: Writing – review & editing, Formal Analysis, Conceptualization.

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## Conflict of interest

JH serves on the advisory board and speaker bureau for Pharming, is an advisory board member and research grant

recipient from the Immune Deficiency Foundation, a research grant recipient from the Jeffrey Modell Foundation and Takeda.

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.

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