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Case Report

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A case of granulomatous lymphocytic interstitial lung disease considered as sarcoidosis

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ABSTRACT

Inborn errors of immunity, formerly known as primary immunodeficiency disorders, are genetic disorders comprising 10 groups and over 500 diseases. Common variable immunodeficiency is the most common symptomatic IEI in adults and is characterised by decreased immunoglobulin levels and recurrent infections after secondary causes of hypogammaglobulinaemia have been ruled out. Granulomatous lymphocytic interstitial lung disease is a distinct clinical entity associated with common variable immunodeficiency and is characterised by lymphoid proliferation and granuloma formation in the lung interstitium. It may resemble sarcoidosis in many clinical, radiological, and pathological features. However, an important distinction is that hypogammaglobulinaemia, i.e., immunodeficiency, is rarely seen in sarcoidosis. A case of primary immunodeficiency presenting with granulomatous lymphocytic interstitial lung disease, in which hypogammaglobulinaemia was detected during follow-up for sarcoidosis, is presented.

Keywords: IEIs, GLILD, hypogammaglobulinemia, CVID, sarcoidosis

INTRODUCTION

Inborn errors of immunity (IEIs) are clinically characterized by increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and malignancy. AmongIEIs, primary antibody deficiencies (PADs) have a better prognosis and longer survival and are the most commonly diagnosed in adulthood. These disorders primarily involve B cell abnormalities, leading to decreased B cell numbers, impaired antibody production, or both.[1] Common variable immunodeficiency (CVID) is the most prevalent symptomatic IEIs in adults, characterized by decreased immunoglobulin levels and recurrent infections following the exclusion of secondary causes of hypogammaglobulinemia.[2] CVID presents with a broad clinical spectrum, encompassing not only recurrent infections but also autoimmune manifestations, malignancies, and particularly interstitial lung diseases (ILDs).[3] Before establishing a diagnosis of noninfectious CVID-associated lung disease, infectious complications must be excluded. Among ILDs, granulomatous lymphocytic interstitial lung disease (GLILD) is a distinct clinical entity predominantly associated with CVID, characterized by lymphoid proliferation and granuloma formation within the lung interstitium.[4] GLILD is a significant cause of morbidity and early mortality in CVID patients.[5,6]

Although several large IEIs patient registries have been established globally[7] defining the precise epidemiology of GLILD remains challenging due to various limitations. However, cohort data estimate that GLILD occurs in approximately 8–20% of CVID patients.[8,9] Some clinical and pathological features of GLILD resemble sarcoidosis-like conditions, as both involve granuloma formation due to immune dysregulation. Both are systemic granulomatous diseases that primarily affect the lungs and lymph nodes, making them difficult to differentiate. If radiological findings suggest GLILD, antibody deficiency can be confirmed through laboratory testing to establish the diagnosis. Here, we present a case of GLILD in IEIs, initially suspected to be sarcoidosis, highlighting the diagnostic challenges of this condition.

CASE

A 38-year-old female patient had a history of intermittent visits to a pulmonologist due to mild shortness of breath and cough persisting for 1.5–2 years. In November 2022, her respiratory symptoms worsened, leading to a diagnosis of asthma. She was prescribed inhaled corticosteroids (ICS) combined with a long-acting beta-2 agonist (LABA) and a montelukast/antihistamine combination, which provided partial symptom relief. A lung computed tomography (CT) scan performed during this period revealed ground-glass opacities and nodules, prompting a preliminary diagnosis of pneumonia and the initiation of antibiotic therapy. Concurrently, oral corticosteroids (OCS) were prescribed due to suspected asthma exacerbation. The patient also received

OCS for 1.5 months, starting in February 2023, reporting partial symptomatic improvement during this period. Her medical history was unremarkable, and she had no history of smoking, atopic conditions, or frequent infections. In a follow-up CT scan conducted in August 2023, non-pathological axillary lymph nodes, mediastinal lymph nodes (maximum diameter: 7 mm), bronchovascular thickening, and ground-glass nodules were observed in both lung parenchymal areas (**Figure 1**). Retrospective analysis of previous CT scans revealed that these lesions were present but had partially regressed in the most recent scan. To establish a definitive diagnosis, the patient underwent diagnostic video-assisted thoracoscopic surgery (VATS) with lung wedge resection and lymph node sampling for pathological examination. Histopathological analysis revealed sharply demarcated nodular infiltration areas in the lung parenchyma, containing multinucleated giant cells and perialveolar lymphocytes forming small nodules. Additionally, granulomatous infiltration with histiocytes and multinucleated cells was noted. Immunohistochemical staining demonstrated zonal CD3 and CD20 positivity in lung nodular lymphocytic infiltration, with B-cell lymphoma-2 (BCL-2) negativity in germinal centers. CD1a staining was negative. The final pathology report described non-necrotizing granulomatous inflammation consistent with interstitial lung disease. Given these findings, the patient was initially suspected of having sarcoidosis. However, upon further immunological evaluation, an antibody deficiency inconsistent with sarcoidosis was detected, and laboratory tests confirmed hypogammaglobulinemia. She was subsequently referred to immunology and allergy departments. Laboratory values and flow cytometry results are detailed in **Table 1, 2**. Abdominal ultrasonography performed for lymphoproliferation screening revealed hepatosplenomegaly. Consequently, intravenous immunoglobulin (IVIG) at 0.6 mg/kg every three weeks and trimethoprim/sulfamethoxazole prophylaxis were initiated. Radiological and pathological findings were considered consistent with GLILD, and additional investigations were conducted. A re-evaluation of the VATS pathology samples confirmed the initial findings. Pulmonary function tests at diagnosis showed a forced expiratory volume in 1 second (FEV1) of 2.38 liters (88%), forced vital capacity (FVC) of 3.02 liters (96%), and FEV1/FVC ratio of 78%. While the patient was under observation without infection, an increase in respiratory symptoms and pancytopenia was noted (**Table 3**). A follow-up high-resolution CT (HRCT) scan revealed the emergence of new pulmonary lesions, with some prior lesions regressing and others progressing, indicative of radiological disease progression (**Figure 2**). Additionally, spleen size increased from 200 mm to 260 mm, and signs of portal hypertension were detected. Bone marrow biopsy performed due to pancytopenia and splenomegaly showed normocellular bone marrow. A carbon monoxide diffusion test (DLCO) was 39%, while pulmonary function tests revealed FEV1 of 2.06 liters (78%), FVC of 2.7 liters (87%), and FEV1/FVC of 76%. A multidisciplinary council recommended upper gastrointestinal endoscopy, colonoscopy, and a repeat bone marrow biopsy. No significant findings were noted in gastrointestinal endoscopic examinations. Consequently, the patient was started on cyclosporine at 50 mg twice daily. After one month of treatment, pulmonary function tests showed FEV1 of 2.14 liters (81%), FVC of 2.7 liters (91%), and DLCO improvement to 57%. Whole-exome sequencing was performed, and results are awaited. The patient remains under follow-up with IVIG and immunosuppressive therapy, maintaining stable health status. A summary of the patient's clinical course is presented in **Figure 3**.

Table 1. The patient's laboratory values

Parameters	Results	References
Ig G	4.1 g/L	7-16 g/L
Ig A	0.03 g/L	0.7-14 g/L
Ig M	0.2 g/L	0.4-2.3 g/L
Ig E	8 IU/ml	5-165 IU/ml
Ig G1	3.01 g/L	4.5-10.01
Ig G2	0.25 g/L	1.69-7.86 g/L
Ig G3	0.35 g/L	0.11-0.85 g/L
Ig G4	0.021 g/L	0.03-2.01 g/L
WBC	$4.2x10^3$/ml	$3.8-11.8x10^3$/ml
Hgb	13.1 g/L	10.9-14.3 g/L
Platelet	$153x10^3$/ml	$179-408x10^3$/ml
Lymphocyte	$0.9x10^3$/ml	$1.1-3.1x10^3$/ml
Calcium	8.5 mg/dl	8.8-10.6 mg/dl

Ig: Immunoglobulin, WBC: White blood cell, Hgb: Hemoglobin g: Gram, mg: Miligram, L: Liter, dl: Deciliter, U: Unit, IU: International unit, µl: Microliter

Table 2. Flow cytometry results

Paremeters	Results%	References
CD45+CD19+ B cell	4	3,4-15.9
Switched **m**emory B cell	1	5.9-34.5
CD16+/CD21 **l**ow B cell	21	1.2-14.2
Naive B cell	67	33.7-79.2
CD45+ CD16 +	11	3.5-28.9
CD45+ CD56 +	6	5.1-24.7
Memory B cell	32	11.2-66.1

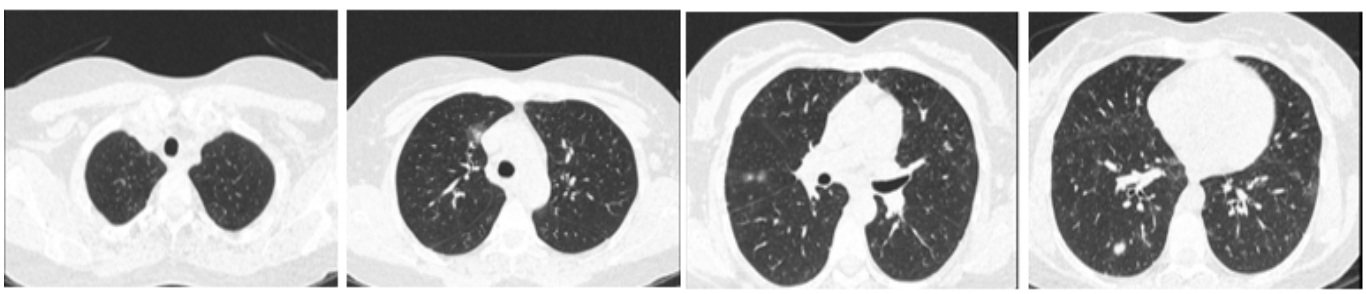

Figure 1. Images at the time of diagnosis

Table 3. Blood results from lymphoproliferative progression

Paremeters	Results	References
WBC	3.0x10³/ml	3.8-11.8 x10³/ml
Hgb	10 g/L	10.9-14.3 g/L
Platelet	72x10³/ml	179-408 x10³/ml
Lymphocyte	1.0x10³/ml	1.1-3.1 x10³/ml

WBC: White blood cell, Hgb: Hemoglobin, L: Liter

DISCUSSION

We present a case of a patient initially followed up with a preliminary diagnosis of sarcoidosis, who was subsequently diagnosed with CVID upon the detection of hypogammaglobulinemia. The patient exhibited clinical, radiological, and pathological pulmonary involvement consistent with granulomatous-lymphocytic interstitial lung disease (GLILD). In addition to GLILD, the patient had concurrent cytopenia and lymphoproliferation, making this an exemplary case where immunosuppressive therapy was initiated.

Sarcoidosis typically occurs in immunocompetent individuals, whereas GLILD is a pulmonary manifestation of IEIs such as CVID. Therefore, in cases where radiological and clinical differentiation between these two conditions is challenging, the presence of hypogammaglobulinemia, impaired vaccine responses, and frequent recurrent infections strongly suggests an underlying IEIs. Although our patient exhibited histopathological and radiological features consistent with sarcoidosis, the presence of hypogammaglobulinemia, low switched memory B cells, and impaired vaccine responses supported the diagnosis of GLILD.

GLILD is a recently recognized disease within the spectrum of IEIs and has been less extensively studied than sarcoidosis. The fact that GLILD may be the initial manifestation of CVID complicates its diagnosis.[10] Additionally, both diseases are systemic granulomatous conditions that primarily affect the lungs and lymph nodes, often presenting with nonspecific symptoms such as cough, exertional dyspnea, and constitutional symptoms.[11] The diagnosis can be easily overlooked, particularly when the clinical picture is not accompanied by frequent infections or if immune deficiency is not suspected. Notably, a significant proportion of patients with either disorder remain asymptomatic.[12–14]

In our case, respiratory symptoms were mild, and the findings observed on high-resolution computed tomography

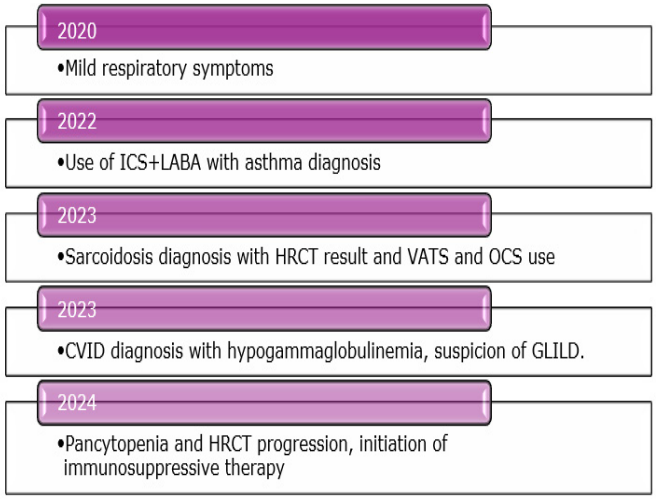

Figure 3. Chronology of the patient's clinical condition

(HRCT) prompted further investigation, aligning with existing literature. Furthermore, the lack of a linear correlation between the severity of radiological involvement and clinical symptoms was notable. While spontaneous remission is common in sarcoidosis, this phenomenon has not been described in GLILD.[15] In our patient, there was no evidence of spontaneous remission, and the development of lymphoproliferative manifestations, including worsening respiratory symptoms, pancytopenia, and progressive splenomegaly, underscored the need for additional treatment.

Autoimmune cytopenia is the most frequently observed immune-mediated complication of CVID, occurring in approximately 10.4% of patients overall and in 59.6% of those with GLILD.[16,17] In our case, cytopenia was a coexisting feature of GLILD. Although no standardized treatment protocol has been established for GLILD, oral glucocorticoids are commonly used as first-line therapy.[18] However, many patients exhibit a suboptimal response to corticosteroids, and recent evidence suggests that a combination of rituximab and azathioprine may be the most effective initial treatment.[19] Our patient had previously used oral corticosteroids (OCS), but treatment was discontinued during follow-up. Given the persistently low diffusing capacity of the lungs for carbon monoxide (DLCO) and worsening respiratory symptoms, additional treatment beyond intravenous immunoglobulin (IVIG) was deemed necessary. Considering the concurrent cytopenia, cyclosporine was initiated following a multidisciplinary council discussion.

Data on the long-term prognosis of CVID and GLILD remain limited. Studies have reported significantly reduced survival rates in CVID patients with GLILD compared to

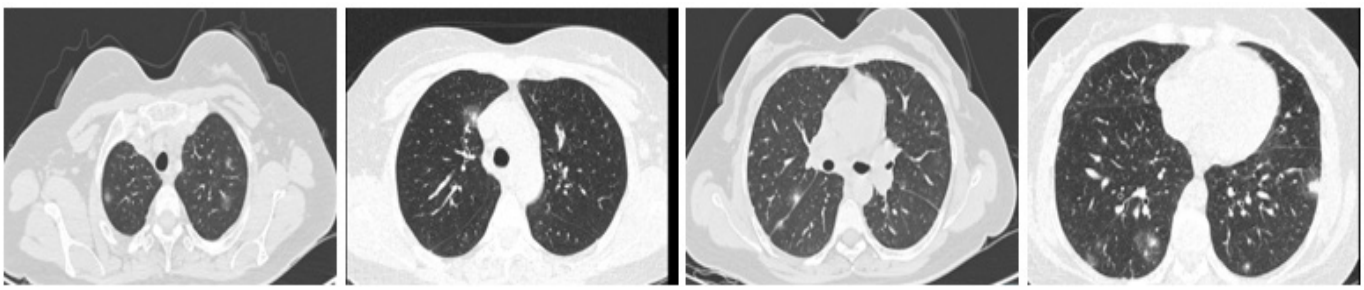

Figure 2. Images with progression

those without.[11] Untreated GLILD has been associated with progressive respiratory dysfunction and eventual respiratory failure. Furthermore, the presence of fibrosis has been identified as a poor prognostic factor.[20] The absence of fibrosis in our patient's serial HRCT scans is a promising finding in terms of long-term respiratory function and prognosis.

CONCLUSION

As a result, this case highlights the importance of considering GLILD in the differential diagnosis of sarcoidosis, as sarcoidosis remains a diagnosis of exclusion. Given the significant overlap in clinical and radiological findings, the presence of hypogammaglobulinemia should prompt further immunological evaluation. Importantly, primary immunodeficiency can be diagnosed based on ILD alone, even in the absence of frequent infections.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

Concept: L.Ç.; Design: L.Ç., N.Ş., G.Ö.; Control: L.Ç., G.Ö., S.D., M.E.; Resources: L.Ç., M.E., G.Ö.; Materials: L.Ç, S.D.; Data Collection and/or Processing: M.E., N.Ş., L.Ç., S.D.; Analysis and/or Interpretation: N.Ş., L.Ç., M.E. Literature Review: L.Ç., S.D., G.Ö.; Writing the Article: L.Ç., S.D. G.Ö.; Critical Review: L.Ç., M.E., G.Ö., N.Ş.

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