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Hidden granulomatous-lymphocytic interstitial lung disease (GLILD): A missed diagnosis in granulomatous and interstitial lung diseases

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Dear Editor,

Granulomatous-lymphocytic interstitial lung disease (GLILD) is a notable complication of common variable immunodeficiency (CVID) and is considered the pulmonary manifestation of systemic immune dysregulation. The clinical presentation of GLILD varies widely; while some patients remain asymptomatic, others may experience non-specific respiratory symptoms such as cough and exertional dyspnea (1). It is estimated to occur in approximately 10–20% of individuals with CVID and has been associated with a more than 50% reduction in life expectancy among adults, with median survival decreasing from 28.9 to 13.7 years after diagnosis (2). Despite the establishment of several extensive registries for patients with primary immunodeficiency (PID) worldwide, methodological limitations have hindered precise epidemiologic characterization of GLILD; however, cohort studies report a prevalence of approximately 8–20% among patients with CVID (3–5). In 2017, the British Lung Foundation and the United Kingdom PID Network defined GLILD as a distinct clinico-radiologic-pathologic entity characterized by lymphocytic infiltration and/or granulomatous inflammation of the lung after exclusion of alternative diagnoses (Table 1) (6). Typical HRCT findings include small or large nodules, consolidations, and ground-glass opacities with lower lobe predominance. Although histopathological confirmation via Video-Assisted Thoracic Surgery (VATS), transbronchial, or

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Table 1. Proposed diagnostic criteria for GLILD	
Step	Requirement/Recommendation
1	CVID or a related primary antibody deficiency.
2	HRCT demonstrating findings consistent with interstitial lung disease, such as nodules, ground-glass opacities, reticulation, or mediastinal/hilar lymphadenopathy.
3	Pulmonary function tests indicating a restrictive pattern and/or reduced DLCO.
4	Exclusion of alternative causes, including infections, malignancies (especially lymphoma), other interstitial lung diseases, and granulomatous disorders such as sarcoidosis.
5	Histopathological confirmation by lung biopsy showing lymphocytic and/or granulomatous inflammation (e.g., non-necrotizing granulomas, peribronchiolar lymphoid infiltrates, organizing pneumonia).
6	Final diagnosis established through an integrated clinico–radio–pathologic assessment by a multidisciplinary team.
CVID: Common variable immunodeficiency, HRCT: High-resolution computed tomography, DLCO: Diffusing capacity of the lung for carbon monoxide.	

percutaneous biopsy remains the diagnostic gold standard, the presence of three of four characteristic histologic features—lymphocytic and peribronchiolar inflammation, non-necrotizing granulomas, and organizing pneumonia—is highly supportive of the diagnosis. Immunoglobulin replacement therapy (IgRT) is the cornerstone of CVID management and should be optimized before initiating immunosuppressive treatment for GLILD, as it effectively reduces respiratory infections. Immunosuppressive therapy is not required in all patients; asymptomatic individuals with stable pulmonary function may be monitored without additional treatment. Corticosteroids remain first-line therapy for symptomatic or progressive disease, while azathioprine and mycophenolate mofetil may be used as steroid-sparing agents in refractory or intolerant cases (6,7). Rituximab is an alternative option for patients with disease progression despite conventional therapy (8–10). We aimed to present two cases diagnosed with GLILD based on clinical and diagnostic evaluations, in whom treatment was subsequently initiated.

A 44-year-old female patient was first admitted in 2008 with cough, fatigue, and night sweats and was initially treated for a presumed lower respiratory tract infection. Subsequent imaging revealed lymphadenopathy and splenomegaly, leading to splenectomy, which demonstrated granulomatous splenitis. A presumptive diagnosis of tuberculosis resulted in a nine-month anti-tuberculosis regimen without clinical improvement.

Thoracic computed tomography (CT) later revealed diffuse bronchiectasis, acinonodular infiltrates, and mediastinal lymphadenopathy, while positron emission tomography - computed tomography (PET-CT) showed increased Fluorodeoxyglucose (FDG) uptake. The patient was subsequently diagnosed with sarcoidosis in 2009 and received intermittent systemic corticosteroid therapy until 2019. In 2022, thoracic CT demonstrated subcarinal lymphadenopathy and nodular ground-glass opacities, and Endobronchial Ultrasound (EBUS) cytology revealed benign lymphoid aspirates. Given the family history of consanguinity and granulomatous disease, immunologic evaluation was performed, revealing hypogammaglobulinemia, lymphopenia, decreased CD4/CD8 ratio, and reduced switched memory B cells (Table 2). CVID was confirmed, IgRT was initiated, and pulmonary findings were consistent with GLILD (Figure 1). The patient remains clinically stable under regular follow-up.

The second case involved a 41-year-old male patient with a 15-year history of CVID receiving regular IgRT who presented with cough, dyspnea, and fever. Thoracic CT revealed bilateral pleural effusions and multiple irregular peripheral consolidations with interlobular septal and peribronchovascular thickening, fissural irregularities, and scattered ground-glass opacities, representing marked progression compared with prior imaging (Figure 2). Abdominal CT demonstrated ascites and splenomegaly. Serologic

Table 2. Summary of the patients' laboratory parameters										
Patients	IgG (g/L)	IgA (g/L)	IgM (g/L)	Lym (cell/ μ L)	CD3 (%)	CD4 (%)	CD8 (%)	CD16-56 (%)	CD19 (%)	CSM-B (%)
Case 1*	3.2↓	<0.25↓	0.82↓	1090↓	67	26.2↓	50.2↑	14.5	5.4	3.59↓
Case 2**	5.1↓	<0.23↓	0.34↓	810↓	64	21.4↓	48.6↑	15.5	4.8	2.68↓
*: A 44-year-old female patient, **: A 41-year-old male patient, CSM-B: Switch memory B CD19+ CD27+ IgD – IgM –, Lym: Lymphocyte, IgA: Immunoglobulin A, IgG: Immunoglobulin G, CD: Cluster of differentiation.										

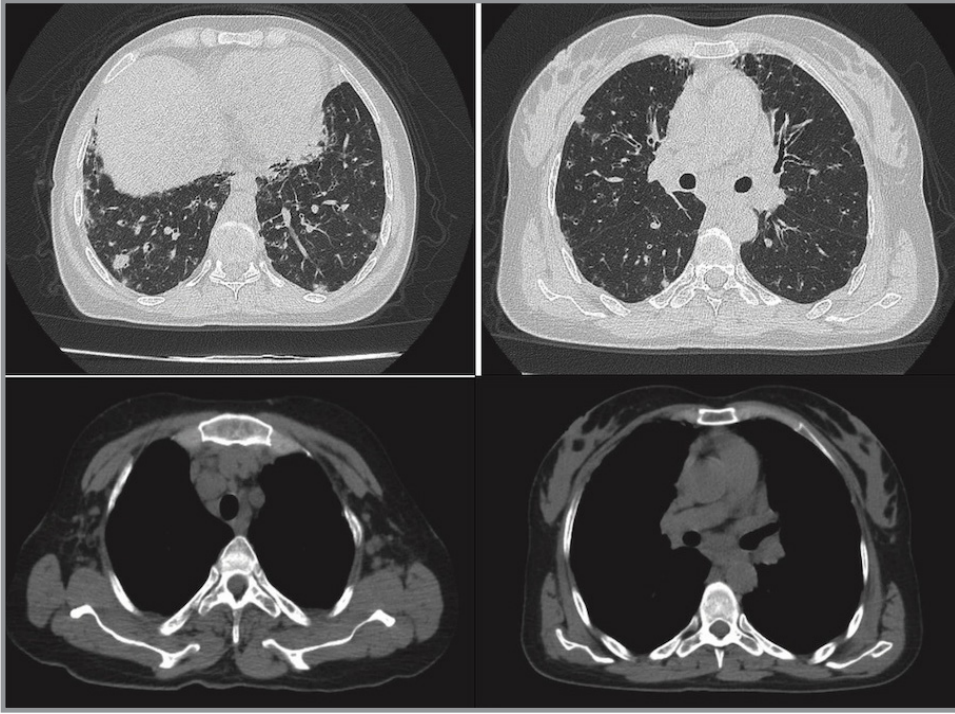


Figure 1. Thoracic CT images of the first case.

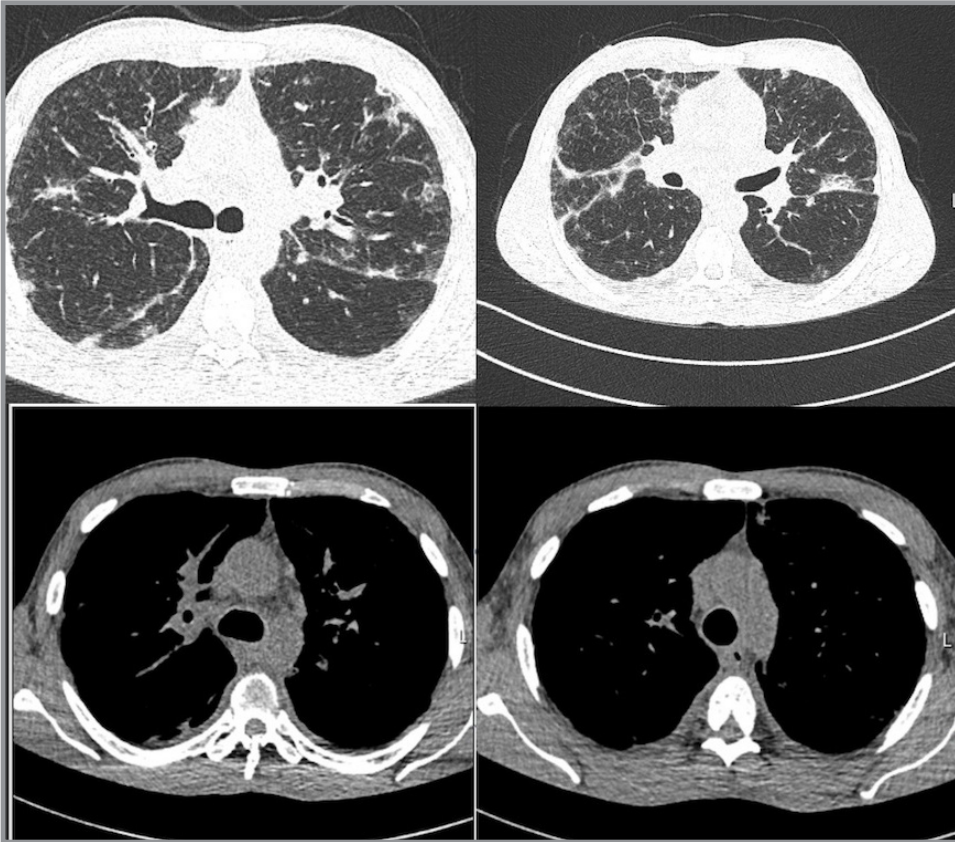


Figure 2. Thoracic CT images of the second case.

testing for rheumatologic disease was negative (Table 2). CT- and ultrasound-guided tru-cut lung biopsy revealed lymphocytic interstitial pneumonia, diffuse interstitial fibrosis, and chronic fibrous pleuritis with dense lymphoplasmacytic infiltration, type II pneumocyte hyperplasia, and focal granuloma-like histiocytic aggregates. Epstein–Barr Virus (EBV) in situ hybridization was negative, excluding lymphomatoid granulomatosis. In the context of underlying CVID and histopathologic findings, a diagnosis of GLILD was established.

In patients suspected of having GLILD, the diagnostic process is inherently interactive and dynamic, requiring the integration of clinical, radiologic, and pathologic data through a multidisciplinary approach. Given the risk of misdiagnosis and the complexity of management, early referral to specialized centers involving both interstitial lung disease and immunology-allergy units is of critical importance.

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CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: All of authors

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