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A 51-Year-Old Man With Unresolved Pulmonary Infiltrates Following *Streptococcus pneumoniae* Pneumonia

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CASE PRESENTATION: A 51-year-old man presented to the clinic 8 weeks after a 6-day hospital admission for severe multilobar pneumonia caused by *Streptococcus pneumoniae*. His productive cough resolved after antibiotics, but he reported persistent dyspnea. He recounted a lifelong history of recurrent sinusitis but no previous episodes of pneumonia. The patient denied fever, weight loss, or tobacco, alcohol, or drug use. He worked as an upholstery craftsman with no work-related exposures. He had no bird or exotic animal exposures, and no history of travel outside Sacramento, California, where he lived. Aside from the recently completed 2-week course of levofloxacin, he was not taking any medications.

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Physical Examination Findings

The patient's vital signs were normal. He had crackles at the right lung base and marked splenomegaly without hepatomegaly. The remainder of his examination was normal.

Diagnostic Studies

Results of a CBC count with differential, liver function tests, and basic metabolic panel were normal. The patient's blood work was notable for decreased levels of IgG (223 mg/dL; normal range, 700-1,600 mg/dL), IgM (< 25 mg/dL; normal range, 63-277 mg/dL), and IgA (< 6 mg/dL; normal range, 69-382 mg/dL). Bacterial and mycobacterial sputum cultures were obtained. Results of pulmonary function testing showed a total lung capacity 70% predicted, FEV_1 79% predicted, and diffusing capacity for carbon monoxide 67% predicted.

A CT scan of the patient's chest revealed mediastinal lymphadenopathy (unchanged from 2 years previously) and splenomegaly. Evaluation of the lung fields showed lower lobe-predominant, faint ground-glass opacities with diffuse bronchocentric nodules seen within the same areas. There was no evidence of consolidation, mosaic attenuation, or masses (Fig 1). Results of bacterial and mycobacterial sputum cultures were negative. BAL of the right lower lobe showed 580 white blood cells/mm^3 (4% neutrophils, 51% lymphocytes, 9% macrophages, and 3% eosinophils) and negative findings on bacterial, mycobacterial, and fungal cultures. Transbronchial biopsy specimens revealed lymphocytic interstitial infiltrates with evidence of fibrosis. Because the findings on bronchoscopy, biopsy, and imaging were not consistent with infection, a surgical wedge biopsy was therefore pursued. Results of a surgical biopsy of the left lower lobe revealed organizing pneumonia with mild submucosal fibrosis, peribronchiolar metaplasia, lymphocytic interstitial infiltrates, and poorly formed, airway-centered granulomas (Fig 2).

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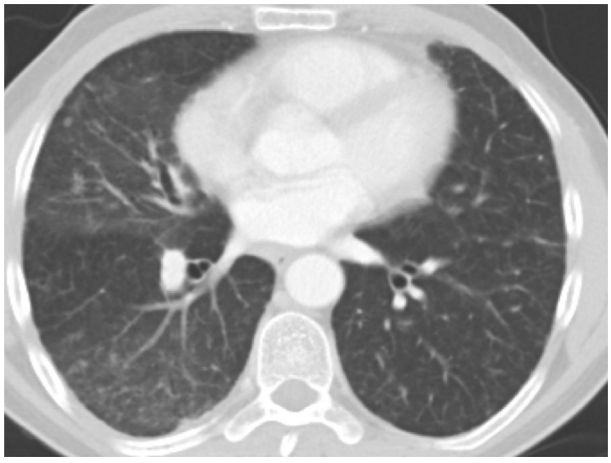

Figure 1 – *CT chest scan showing a lower lobe-predominant, fine reticular pattern with ground-glass and peribronchial nodules.*

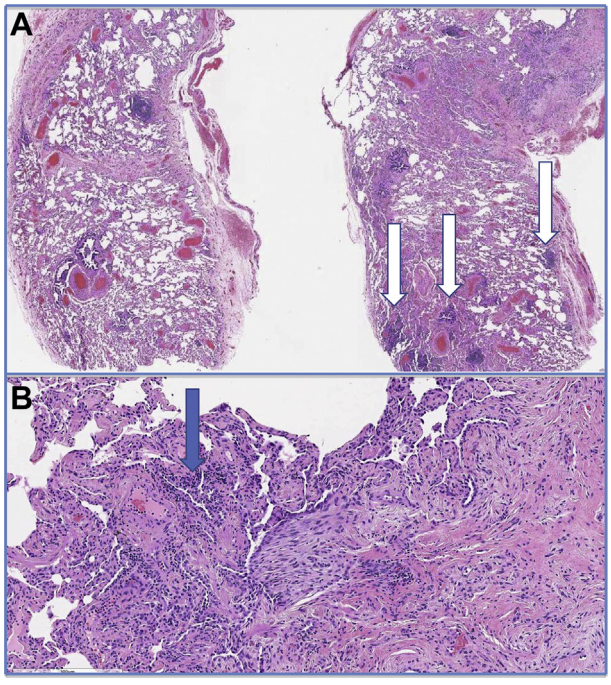

Figure 2 – *Right lower lobe surgical biopsy samples from video-assisted thoracoscopic surgery with gross specimen: A, loosely formed, non-caseating granulomas (white arrows); and B, peribronchial lymphocytic infiltrates (blue arrow). Intraoperative cultures did not reveal bacterial, mycobacterial, or fungal etiology.*

What is the diagnosis?

Diagnosis: Common variable immunodeficiency with granulomatous lymphocytic interstitial lung disease.

Discussion

Common variable immunodeficiency (CVID) is a primary immunodeficiency syndrome resulting from various genetic defects leading to impaired B-cell differentiation, characterized by reduced serum concentrations (beyond two SDs of normal) of IgG and IgA or IgM, anergy to antigen presentation/vaccination, and lack of another immunodeficiency state. CVID affects all age groups, with an estimated prevalence of 1 in 25,000 individuals. Classically, patients present with recurrent sinopulmonary bacterial infections but may also experience pneumonia, GI infections, arthritis, meningitis, and sepsis. These patients are particularly susceptible to infection with encapsulated bacteria, including *S pneumonia* and *Haemophilus influenzae*. Treatment of CVID includes IV immunoglobulin augmentation to prevent and control recurrent infections.

Although antibody deficiencies are most apparent, T-cell abnormalities occur in many patients with CVID, which may explain the increased rate of lymphoproliferative diseases and autoimmunity seen with the disorder. With the advent of immunoglobulin infusions, death from infection has decreased. Noninfectious complications, including granulomatous lymphocytic interstitial lung disease (GLILD), are becoming increasingly important in the management of patients with CVID. Patients present with GI disorders, including chronic diarrhea with observed inflammatory bowel disease and GI lymphoma, autoimmune disease, and malignancies, including non-Hodgkin's lymphomas. Lung manifestations include bronchiectasis, recurrent pneumonia, and interstitial lung disease, including GLILD.

GLILD describes a spectrum of infiltrative pulmonary complications found in patients with CVID characterized by granulomatous and lymphoproliferative histologic patterns. Patterns associated with GLILD include lymphocytic interstitial pneumonia, lymphoid hyperplasia, follicular hyperplasia, and a sarcoidosis-like granulomatous disease. Peribronchiolar and interstitial lymphoid infiltration have been described as the predominant histologic patterns. GLILD has been increasingly identified now that infectious complications of CVID have been mitigated by immunoglobulin infusions, with an estimated incidence of 10% to 25% of patients with CVID.

The pathogenesis of GLILD remains incompletely understood; study is difficult due to the heterogenous presentations of disease as described earlier. Although agammaglobulinemia is a defining characteristic in CVID, it is unlikely to be the cause of GLILD. X-linked agammaglobulinemia, a similar immunodeficiency defined by the absence of immunoglobins (but immunologically differentiated from CVID by the former having functional T cells), does not lead to GLILD. Many proposed mechanisms exist regarding the pathogenesis of GLILD: immune complex deposition, dysregulated T-cell response to chronic antigenic stimulation, dysfunctional memory B cells, upregulation of tumor necrosis factor, and viruses (Epstein-Barr, types of HIV, and human herpesvirus 8).

GLILD commonly presents with indolent dyspnea and cough in the absence of active infection, with fever and pleuritic chest pain less commonly reported. History and examination may also show splenomegaly, lymphadenopathy, and GI/hepatic disease, presumably related to granulomatous infiltration. Results of pulmonary function testing typically reveal a restrictive pattern with an impaired diffusing capacity. Typical CT findings include pulmonary nodules, smooth interlobular septal thickening, lymphadenopathy, ground-glass attenuation, and focal consolidations. Fine and coarse reticulation can be seen, which is indicative of mild fibrosis. Adenopathy can be seen in the hilum/mediastinum and the extrathoracic space (eg, soft tissue, abdominal) and is often found to fluctuate in size over time. BAL typically reveals lymphocytosis with no evidence of infection.

Results of transbronchial biopsies can reveal granulomas and strongly suggest GLILD in the correct clinical context. Surgical excisional lung biopsies are generally required for the definitive diagnosis of GLILD to exclude alternative causes of diffuse parenchymal interstitial lung disease and lymphoproliferative diseases. Canonical histopathologic patterns of GLILD include lymphoid interstitial pneumonia, lymphoid hyperplasia, follicular bronchiolitis, and noncaseating granulomatous disease similar to sarcoidosis. There is often a spectrum of findings involving lymphocytic and granulomatous proliferation, predominantly in the airways.

There is no standard therapy for GLILD, although corticosteroids are frequently used. Both T-cell (eg, cyclosporine, azathioprine, 6-mercaptopurine) and B-cell (eg, rituximab) and tumor necrosis factor alpha–targeted (eg, infliximab) suppressive agents have been used with anecdotal success. Several studies have found that GLILD is associated with higher mortality; one such study was a large retrospective analysis of 68 patients with CVID that reported a median survival of 13.7 vs 28.8 years for patients with and without GLILD, respectively. Whether treatment improves survival in patients with GLILD is unknown.

Clinical Course

The study patient presented with pneumococcal pneumonia and was found to have persistently low immunoglobulin levels on repeat testing in the absence of other immunodeficiency states, thus establishing the diagnosis of CVID. The fine ground-glass and peribronchial nodules were consistent with potential GLILD. Although the imaging and transbronchial biopsy specimens were suggestive of GLILD, they were not diagnostic, and results of a surgical biopsy also aided in ruling out other lymphoproliferative diseases. These findings, in the clinical context of the patient's persistent dyspnea despite negative culture findings and no suggestive active infection, prompted a surgical lung biopsy. The pathologic findings from the video-assisted thoracoscopic surgical biopsy revealed the presence of granulomas, organizing pneumonia, and lymphocytic infiltrates, fitting the spectrum of findings that can be seen in GLILD. The patient was started on chronic IV immunoglobulin infusions for his CVID and prednisone 0.5 mg/kg for his GLILD. This treatment led to symptomatic, radiographic, and pulmonary function improvement within a matter of months. The patient was ultimately transitioned to 6-mercaptopurine for long-term steroid-sparing immunosuppression.

Clinical Pearls

1. *As many as 10% to 25% of patients with CVID will develop GLILD.*
2. *GLILD may be suggested on imaging, but definitive diagnosis requires bronchoscopic or surgical biopsy.*
3. *GLILD encompasses a spectrum of histopathologic patterns with no evidence of active infection, including lymphocytic interstitial pneumonitis, follicular bronchiolitis, lymphoid hyperplasia, organizing pneumonia, and a sarcoidosis-like pattern of noncaseating granulomatous inflammation.*
4. *The pathogenesis of GLILD is not well understood but is believed to involve both B- and T-cell dysregulation, possibly secondary to immune complex deposition, T-cell dysregulation, memory B-cell dysregulation, high levels of tumor necrosis factor, and/or human herpesvirus 8.*
5. *GLILD portends a worse prognosis than CVID alone.*
6. *Corticosteroids and other immunosuppressant agents have been used for the treatment of GLILD, although supporting evidence is largely anecdotal.*

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Suggested Readings

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