

Granulomatous Lymphocytic Interstitial Lung Disease

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KEYWORDS

- Common variable immunodeficiency • Interstitial lung diseases • Granuloma
- Sarcoidosis • Lymphoproliferative disorders

KEY POINTS

- GLILD is a distinctive manifestation of CVID and is characterized by a combination of granulomatous and lymphoproliferative interstitial features.
- Confident diagnosis of GLILD can be challenging and requires a multidisciplinary approach.
- Other causes of granulomatous and lymphoproliferative lung disorders must be definitively excluded before a GLILD diagnosis is rendered.
- On imaging, in contrast to sarcoidosis, GLILD findings commonly demonstrate a mid and lower lung zone predominance.
- In GLILD, pulmonary nodules are common and tend to wax and wane.
- Immunosuppressive treatment is generally reserved for patients with GLILD with persistent respiratory symptoms or evidence of radiographic or physiologic progressive lung disease.

INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous syndrome characterized immunologically by hypogammaglobulinemia and impaired antibody response. It is the most common of the primary immune deficiencies, and clinically characterized by a host of systemic manifestations, including recurrent sinopulmonary infections, autoimmune disorders, and lymphoproliferation. The pulmonary manifestations of CVID may be infectious or noninfectious (**Box 1**). The infectious complications are more common and must be excluded before a noninfectious, CVID-associated, pulmonary diagnosis is rendered. Examples of infectious complications include

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Box 1**Pulmonary complications in CVID**

Infectious disorders

- Primary infections
 - Bacterial, fungal, and viral pneumonias
 - Granulomatous lung disease (eg, nontuberculous mycobacteria)
- Recurrent or postinfectious
 - Bronchitis
 - Bronchiectasis
 - Bronchiolitis
 - Cavitory and bullous lung disease

Noninfectious disorders

- ILD
 - GLILD
 - Idiopathic concurrent disorders (eg, UIP)
- Neoplastic disorders
 - Primary malignancy (eg, primary pulmonary lymphoma)
 - Secondary malignancies (eg, secondary lymphomatous spread from neighboring sites, such as mediastinal lymph nodes)
- Primary airway-centered disorders^a (eg, follicular bronchiolitis)
- Isolated benign local (eg, NLH) or diffuse lymphoproliferative disorders (eg, LIP)

Mixed infectious and noninfectious disorders

Abbreviations: CVID, common combined immunodeficiency disorder; ILD, interstitial lung disease; LIP, lymphocytic interstitial pneumonia; NLH, nodular lymphoid hyperplasia; UIP, usual interstitial pneumonia.

^a Might be associated with hyperreactive airway disease.

bronchiectasis, cavities, and postinfection scarring. Noninfectious manifestations can be subdivided into primary (eg, pulmonary MALToma) or secondary malignancies (eg, pulmonary involvement from neighboring sites, such as mediastinal lymphoma); airway-limited entities (eg, follicular bronchiolitis); parenchymal or interstitial lung disease (ILD); and benign lymphoproliferative disorders (eg, nodular lymphoid hyperplasia [NLH]). Although patients with CVID have anecdotally been reported to develop ILD in a variety of pathologic patterns,¹⁻⁴ granulomatous-lymphocytic ILD (GLILD) is unique to CVID. The classic histopathologic pattern of GLILD is a cellular interstitial pneumonia with a combination of granulomatous and lymphoproliferative (a combination of lymphocytic interstitial pneumonia [LIP], follicular bronchiolitis, and lymphoid hyperplasia) features.³ However, in some patients only lymphoproliferative changes are found, whereas in others granulomatous inflammation dominates. Thus, arriving at a confident diagnosis of GLILD can be challenging and requires a multidisciplinary approach with thoughtful integration of clinical, radiologic, and physiologic data. This article focuses on the diagnosis and management of GLILD.

PREVALENCE

The prevalence of ILD in one retrospective analysis of 69 patients with CVID was 26% (18 of 69), and more than two-thirds of these had GLILD.³ However, larger-scale epidemiologic data for GLILD are unknown.²

DIAGNOSTIC EVALUATION

Clinical Evaluation

In patients with known CVID, the development of respiratory symptoms or signs should prompt a focused respiratory evaluation. The clinician embarks on a diagnostic evaluation that includes taking an in-depth medical history with the focus on the severity and course of respiratory symptoms, with special attention to identifying historical features that suggest recurrent respiratory tract infections, the most common presenting feature of patients with CVID. GLILD generally presents insidiously with cough and exertional dyspnea.

Comprehensive occupational and environmental histories, a full systems review, and a thorough physical examination are necessary for an accurate diagnosis. In a patient with recognized CVID without infection, significant environmental exposures or an established diagnosis of connective tissue disease, finding splenomegaly, oligoarticular or polyarticular arthritis, lymphadenopathy, and a nodular pattern on high-resolution chest computed tomography (CT) point strongly toward a diagnosis of GLILD. In contrast, “B” symptoms in a patient with CVID, especially when lung nodules or masses are also identified, raise suspicion for lymphoma.

Because the granulomatous/lymphocytic inflammatory process that leads to GLILD in the lung can affect other organs, screening for evidence of other organ dysfunction is important. Anemia, malabsorption, enteropathies (eg, intestinal NLH), liver disease (eg, secondary to granulomatous infiltration, autoimmune hepatitis, and nodular regenerative hyperplasia), and kidney involvement should all be considered.^{5,6}

In some cases, GLILD is the initial manifestation of CVID. In cases in which CVID is yet to be recognized, there is often delay in making an accurate diagnosis of GLILD.⁷ For example, a patient with nonnecrotizing granulomas in the liver or spleen and bilateral hilar adenopathy with interstitial changes on chest imaging may erroneously be diagnosed with sarcoidosis if CVID goes unappreciated. Thus, an exhaustive search for lymphoproliferative disorders, granulomatous infections (eg, mycobacterial and fungal), and other causes of granulomatous lung diseases, such as drug reactions, occupational exposures (ie, berylliosis), sarcoidosis, hypersensitivity pneumonitis, or vasculitis, must be undertaken before GLILD is diagnosed. The fact that patients with CVID are at risk for developing autoimmune phenomenon and infections further complicates matters: in these patients GLILD may occur before or after diagnosis of another systemic inflammatory disorder (eg, Sjögren syndrome) or granulomatous infection (eg, nontuberculous mycobacterial infection).

In patients with CVID, microbiologic testing should be pursued based on clinical suspicion. Components of the evaluation may include sputum, urine, sinus, stool, synovial fluid (eg, ureaplasma), or blood cultures. When chest imaging reveals parenchymal lung abnormalities, bronchoalveolar lavage (BAL) should be performed to exclude active pulmonary infection. Consultation with an infectious disease specialist is frequently beneficial in addressing potential infectious etiologies.

Pulmonary function testing is useful for quantifying pulmonary impairment and for monitoring response to therapy in GLILD. A mixed obstructive-restrictive defect, or more commonly an isolated restrictive ventilatory defect, with a low diffusing capacity for carbon monoxide is observed in patients with GLILD. However, some patients

(even some with extensive radiologic abnormalities) have normal pulmonary function testing.³ Maximal cardiopulmonary exercise testing can be a valuable tool in the early detection of subtle pulmonary gas exchange abnormalities and in predicting the degree of impairment in functional capacity in subjects with GLILD; however, its limited availability detracts from its usefulness.⁸

Invasive Testing and Histopathology

Besides ruling out infection, bronchoscopy with BAL can be a useful tool in the evaluation of ILD in patients with CVID. Differential cell counts from BAL effluent may hint at the presence of a lymphocytic alveolitis (eg, >25%), consistent with histopathologic lymphoid interstitial pneumonia, one of the key components in the GLILD lesion. Although BAL lymphocytosis can be an important piece in the diagnostic puzzle, it alone does not confirm GLILD. A lymphocyte-predominant BAL may be found in several ILDs, including hypersensitivity pneumonitis, drug-induced lung disease, and sarcoidosis. Flow cytometry and gene rearrangement studies on the effluent may identify the presence of a monoclonal population of lymphocytes, thus confirming lymphoma, which is always a concern in this patient population.^{9,10}

Transbronchial biopsies (TBBx) are potentially useful in the diagnostic evaluation of peribronchovascular processes, such as lymphoma, and in airspace-filling diseases. However, small specimen size and sampling error are significant limitations to TBBx, and in general, a highly confident histopathologic diagnosis of GLILD cannot be made from TBBx specimens. Video-assisted thoracoscopic surgery remains the surgical procedure of choice when a diagnosis cannot be obtained by less invasive methods and when the clinical, physiologic, radiographic, and laboratory features are not specific enough to provide diagnostic confirmation. However, histologic data need to be integrated with clinical and radiographic information to come to a final diagnosis.

Pathologic Patterns

The key histopathologic findings of GLILD (**Fig. 1**) are nonnecrotizing granulomas and a spectrum of lymphoproliferation, including LIP, follicular bronchiolitis, NLH, and low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) or so-called MALToma (extranodal marginal zone B-cell lymphoma). Potentially confusing matters, any of these histopathologic components can be the sole finding, a feature that may be caused by sampling. For example, CVID patients can develop follicular bronchiolitis or LIP without granulomas. I prefer to reserve the term GLILD for those cases in which both granulomas and lymphoproliferative processes occur.

Granulomas

Microscopically, granulomas in GLILD are sarcoid-like, nonnecrotizing, and fairly well circumscribed in a perilymphatic distribution. The granulomas are generally described as morphologically dissimilar to those observed in infection, vasculitides, and hypersensitivity pneumonitis; however, whether this distinction actually can be made in practice has not been tested.

Because CVID predisposes to bacterial infections, special stains for acid-fast bacilli and fungi should be assessed in all cases. Randomly dispersed necrotizing granulomas may be seen (and hint at concomitant infection), but they are not the predominant feature. Localized or systemic nonnecrotizing granulomatous disease has been described in 8% to 20% of patients with CVID.^{11–13} Of this subgroup, the lung is one of the most common involved sites, with granulomas reported to occur in 54% of affected patients.¹² I have found granulomatous inflammation in the livers, kidneys, gastrointestinal tract, and spleens of patients with GLILD.

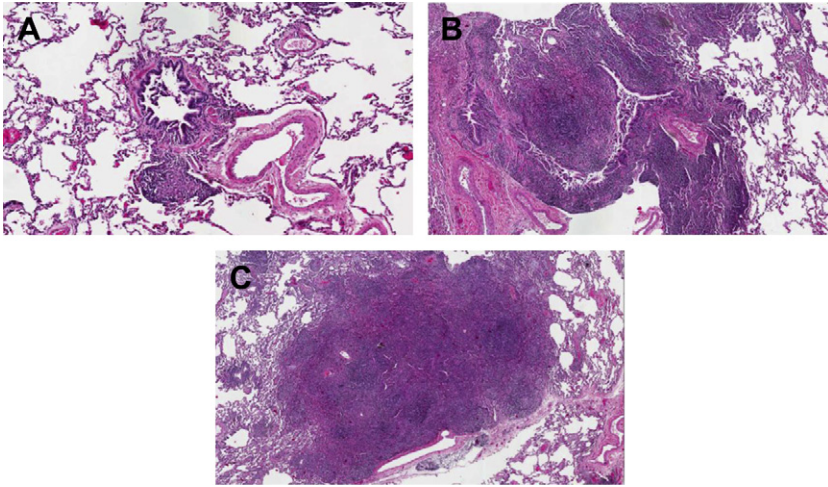


Fig. 1. The pathologic findings in a biopsy-proved patient with granulomatous lymphocytic interstitial lung disease. (A) Peribronchiolar, nonnecrotizing granuloma (hematoxylin and eosin, original magnification $\times 100$). (B) Lymphoid hyperplasia with regions of nodular and conglomerate interstitial, peribronchiolar, and perivascular lymphocytic inflammation (hematoxylin and eosin, original magnification $\times 200$). (C) Lymphoid hyperplasia with germinal centers (hematoxylin and eosin, original magnification $\times 200$).

Lymphoproliferative features

The histologic appearance of LIP in GLILD is no different from LIP of other causes. LIP is characterized by cellular infiltrates composed of a mixture of lymphocytes, plasma cells, and histiocytes that diffusely expand the alveolar septae.^{14,15} The interstitial lymphoid cells are mainly T cells, whereas polyclonal B cells are found in the lymphoid follicles. In LIP, germinal centers are common and sometimes prominent; however, in the setting of CVID they might be few and small.

Follicular bronchiolitis or follicular hyperplasia of bronchus-associated lymphoid tissue is present when the lymphoid infiltrate is limited to the bronchioles and adjacent peribronchiolar interstitium. The infiltrate can be so extensive as to cause bronchiolar obliteration.¹⁶ In contrast to LIP, cellular and lymphoid extension into the distal parenchyma, or widespread alveolar septal infiltration, is not present in follicular bronchiolitis.¹⁵

NLH, sometimes referred as inflammatory pseudotumor, is histologically similar to LIP. However, NLH is a discrete mass lesion usually solitary, whereas LIP is a diffuse interstitial process.¹⁴

Because atypical lymphoid hyperplasia and malignant lymphoproliferative disorders enter the differential diagnosis of LIP, the histopathologic diagnosis of LIP cannot be made solely on morphologic grounds. Therefore, immunohistochemistry for monoclonality or molecular studies is advisable to support the diagnosis. Close clinical, physiologic, and radiographic follow-up with expert thoracic pathologic input is desirable when features of clonality are observed on surgical lung biopsy, because clonal lymphocyte populations can occur in patients with CVID without lymphoma (eg, infection-related atypical lymphoid hyperplasia) or may precede the development of lymphoma.¹⁷ MALT is generally absent from the normal human lung.¹⁸ However, it can be acquired during bronchial inflammatory processes and diseases involving chronic B-cell dysfunction. Acquired MALT tissue in patients with CVID can take the form of a benign lymphoid disorder or MALTomas.¹⁸ MALTomas are the most frequent primary non-Hodgkin's lymphoma in the lungs and are far more prevalent than NLH. In

contrast to LIP, the lymphoid infiltrate in MALTomas is monomorphic and denser, is often found in a lymphangitic distribution, may be associated with destruction of lung architecture, and extend into the parietal pleura and lymph nodes.¹⁴ Unlike non-CVID immunodeficiencies, B-cell-derived lymphoma is rarely an Epstein-Barr virus-driven disease.¹⁷

Radiologic Evaluation

Chest CT findings in GLILD are dynamic. It is unclear if the chest CT pattern in GLILD correlates with other parameters of disease activity (eg, BAL or extrapulmonary manifestations). However, when integrated with clinical data chest CT plays an invaluable role in guiding the selection of invasive testing; helping discriminate the presence of lung fibrosis from other nonfibrotic patterns; in detecting and following specific complications (eg, superimposed cavitory lung lesion); and in assessing the response to therapy in GLILD.

Common chest CT findings in GLILD include multifocal airspace consolidation; smooth thickening of the interlobular septa and widespread centrilobular micronodules (both with lower zone predominance); mediastinal and hilar lymphadenopathy; bronchiectasis; patchy bilateral ground-glass opacities; and sometimes air trapping emanating from inflammatory small airways involvement, mucous plugging, or abnormal airway collapse (**Fig. 2**).^{4,19,20} In more advanced cases, features of fibrosis characterized by fine and coarse reticulation and honeycombing have been observed.¹⁹ Thin-walled cysts in a bronchovascular distribution, as seen often in LIP,²¹ are not a frequent or dominant pattern in GLILD but can be helpful in distinguishing LIP from follicular bronchiolitis or diffuse lymphoma.²² Conglomerate masses surrounding major airways and irregular or beaded bronchovascular bundles common in sarcoidosis are not a characteristic chest CT feature of GLILD.

A common and challenging problem is the waxing and waning of lung opacities in GLILD. Their differential diagnosis includes organizing pneumonia, eosinophilic lung disorders, infectious and noninfectious granulomatous disorders, and lymphoproliferative lesions. The frequently migratory nature of the nodules on serial CT often effectively excludes granuloma, infection, and lymphoma, and suggests organizing pneumonia. Evaluation of the specific morphologic characteristics (size, margins, contour, internal features), growth rate, and surrounding lung parenchyma of solitary or multifocal pulmonary nodules with CT can help differentiate benign from malignant nodules. How these nodules should be followed is unclear but requires striking a balance between diligence (so that malignant transformation to lymphoma is not missed) and exposing the patient to excessive radiation (with repeated CT scans) and multiple lung biopsies.

RISK FACTORS FOR THE DEVELOPMENT OF GLILD

The pathogenesis of GLILD is poorly understood. Although many questions remain, in the last one and half decades observations have uncovered important links between lymphoproliferation, granulomatous disease, and CVID, discussed next. (1) GLILD often occurs in patients with CVID with low switched memory B cells (CD27⁺/IgM⁻/IgD⁻) and CD45RA⁺CCR7⁺CD4⁺T cells. Such patients commonly have a severe clinical phenotype characterized by granulomatous disease, lymphadenopathy, hypersplenism, lymphoid hyperplasia, and chronic lung disease.^{12,23–25} (2) Germinal center presence and dysfunction are prerequisites for the development of GLILD. The inducible costimulator (ICOS) that is found on activated T cells interacts with the ICOS-L receptor on B cells, allowing B cells to undergo class switch recombination

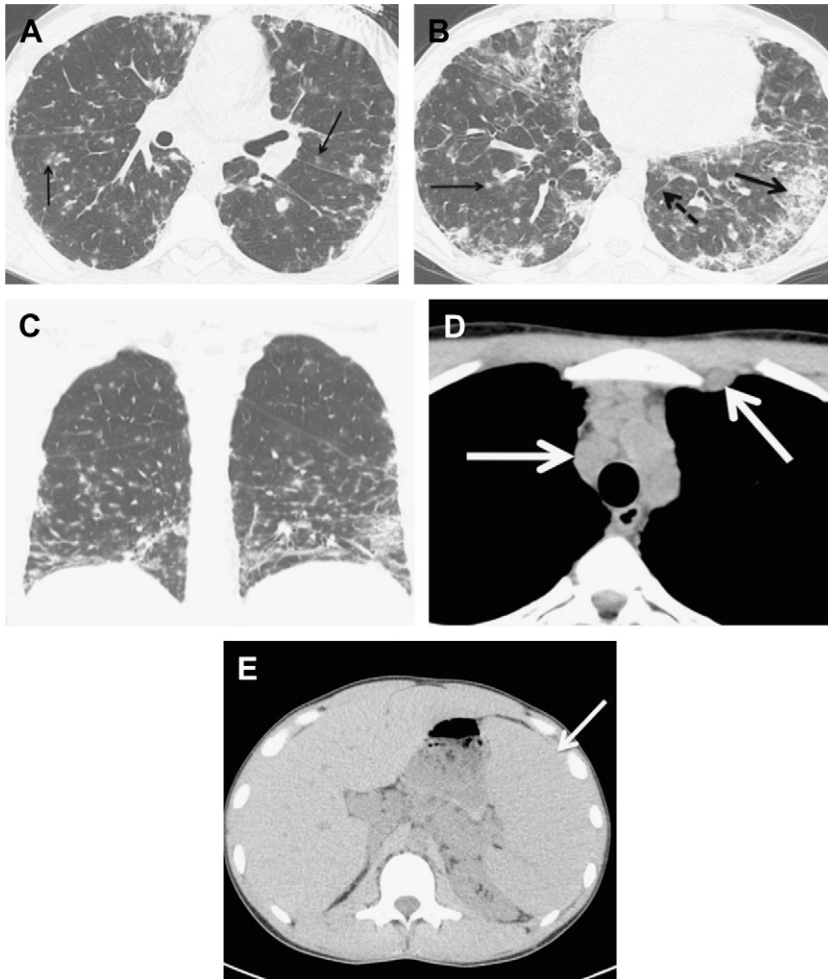


Fig. 2. Noncontrast chest CT in a 29-year-old man with typical findings of granulomatous lymphocytic interstitial lung disease in the setting of combined variable immunodeficiency syndrome. (A, B) Axial noncontrast CT images in lung windows show bronchovascular-predominant pulmonary nodules (*thick arrows*) of variable density. Patchy areas of consolidation (*thin arrows*) are present at the lung bases. Mild interlobular septal thickening (*dashed arrows*) is also noted. (C) Coronal reformation demonstrates the basilar preponderance of disease. (D, E) Axial images in soft tissue windows show paratracheal and left internal mammary lymphadenopathy (*arrows in D*) and splenomegaly (*arrow in E*).

and facilitating the development of follicular T helper cells.^{26,27} ICOS deficiency represents a genetic human defect in which there is severe peripheral B-cell lymphopenia and germinal centers do not form. Therefore, in patients with ICOS deficiency²⁸ and subjects with X-linked agammaglobulinemia (a pure B-cell disorder), GLILD does not occur. Dysfunctional germinal centers provide a distorted cytokine environment for T-cell homeostasis contributing to defective T-cell proliferative responses, abnormal T-cell-dependent antibody responses, antigen sequestration, and granuloma formation.^{11,17,27,29,30} (3) Granulomatous disease in CVID has been linked with

an uncommon tumor necrosis factor (TNF) allele, TNF +488A.³¹ Although, persistent activation of the TNF system has been implicated in the immunopathogenesis of certain CVID subgroups, whether the presence of the TNF +488A allele contributes to high levels of TNF in peripheral blood or BAL and subsequently granulomatous infiltration in GLILD is unknown. (4) Human herpes virus type 8 has been associated with lymphoproliferation and GLILD. In one study, genomic DNA isolated from peripheral blood mononuclear cells, and screened by nested and real-time quantitative polymerase chain reaction for the presence of human herpes virus type 8 genome, was positive in 6 of 9 patients with CVID with GLILD and only 1 of 21 patients with CVID without GLILD.³² (5) The presence of granulomas in CVID has been associated with peripheral blood CD4⁺ lymphopenia, abnormal CD4-dependent immune response, and CD8⁺ lymphocytosis.^{33,34} Although abnormal interferon production in CD8⁺ cells in subjects with CVID has been described,³³ its contribution to granulomatous disease is unclear. Moreover, in sarcoidosis, increased CD4/CD8 ratio and excess CD4⁺ T-lymphocyte activity at sites of disease activity is well documented.^{35,36} Whether the same is observed in CVID-GLILD or alternatively whether there is “paradoxical” CD4⁺ lymphopenia at sites of granuloma formation is unknown.

PROGNOSIS

In patients with CVID, GLILD predicts shortened survival,^{3,37} and when present, respiratory failure is the most common cause of death.^{3,12} This was illustrated in a retrospective study of 69 patients with CVID: subjects with ILD had a median survival of 13.7 years, whereas patients without ILD had a median survival of 28.8 years.³ The prognosis is also linked to the severity of the disease, with severe restrictive lung dysfunction and extensive disease and fibrosis on chest CT being associated with worse outcome.³ Extrapulmonary granulomatous disease is also relevant because when subjects with granulomatous-lymphocytic infiltration in any organ are analyzed, the median survival decreased to 10.9 years.³ Causes of death in this subgroup included end-stage granulomatous liver disease, autoimmune hemolytic anemia, and systemic lymphoproliferative diseases. Early recognition and management of CVID when confronted with newly diagnosed GLILD may also have prognostic implications. Diagnostic delay of CVID is associated with considerable morbidity, particularly recurrent pneumonias, and probably secondary structural lung damage.^{1,7,38,39}

MANAGEMENT

Immunoglobulin replacement therapy should be optimized to provide at near normal range immunoglobulin blood levels to help prevent and reduce the risk for sinopulmonary infections,^{1,38,39} which can trigger GLILD deterioration. In one study of 12 patients with chronic lung disease and antibody deficiency, subjects were randomized to either 0.6 or 0.2 g/kg intravenous immunoglobulin and the frequency of acute infection was substantially reduced when serum IgG was 500 mg/dL or more. Pulmonary function worsened on the low-dose regimen and improved on the high-dose regimen.⁴⁰ Similarly, antimicrobial therapy plays an important role, because immunoglobulin replacement alone may not adequately prevent or treat superimposed lung infections aggravating GLILD.

Early diagnosis and treatment of GLILD might help prevent progressive and debilitating lung disease.⁷ Pharmacologic treatment is generally reserved for those with persistent respiratory symptoms or evidence of radiographic or physiologic progressive lung disease. In this setting, a systemic corticosteroid trial is commonly first used. The dose and duration of corticosteroid therapy remain unknown. Furthermore, the quality

of evidence informing the use of corticosteroids and other agents is very limited and based on observational uncontrolled data. In my practice, I continue corticosteroid therapy, in the absence of adverse side effects, for 3 to 6 months while reassessing the patient's symptoms, subjective exercise tolerance, pulmonary physiology, and chest imaging (**Fig. 3**). Therapy might be continued if there has been improvement (eg, improved dyspnea and pulmonary function, decreased oxygen requirements, and interstitial chest CT findings). To limit steroid-related toxicity and avoid intolerable side effects, steroid-sparing agents may be considered on a case-by-case basis. In refractory cases, the type of lymphocytic infiltration on surgical lung biopsy (eg, B-cell predominant vs T-cell process) and the presence of concomitant disorders, such as idiopathic thrombocytopenic purpura, may argue for the introduction of such agents as rituximab, although data to support its use are extremely limited.

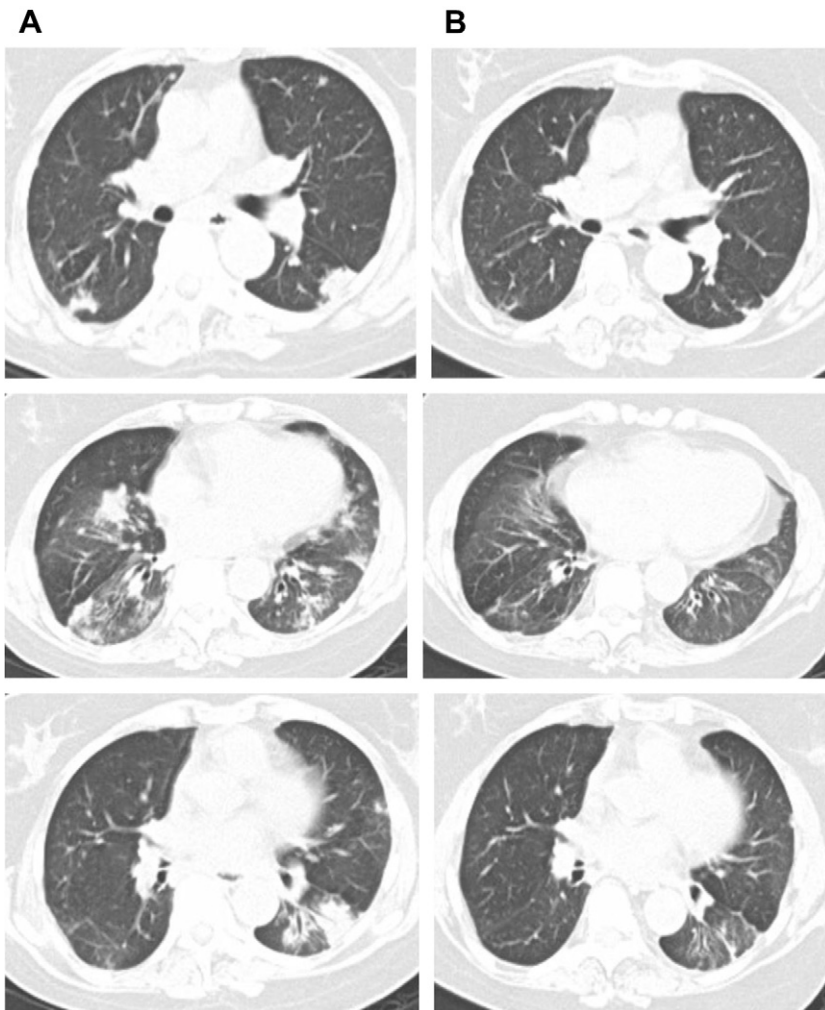


Fig. 3. Noncontrast chest CT in a 60-year-old woman with granulomatous lymphocytic interstitial lung disease before (A) and after 2 months of prednisone therapy (B).

The nonpharmacologic management of GLILD centers on close patient follow-up by a multidisciplinary team that includes pulmonary and allergy/immunology primarily and other subspecialties as indicated by the clinical scenario. Supportive measures include (1) supplemental oxygen when needed; (2) treatment and prevention of comorbid conditions, such as gastroesophageal reflux and bronchiectasis (eg, airway clearance techniques, mucolytic agents, bronchodilators, inhaled corticosteroids, antimicrobial agents); (3) smoking cessation; and (4) maintenance of nutrition and pulmonary rehabilitation therapy. Also, after the decision to initiate immunomodulatory therapy has been made management of potential side effects or complications is highly advisable. Therefore, if corticosteroids are used, screening (eg, periodic electrolytes and bone mineral density testing), prevention (eg, bone mineral-preserving therapies), treatment of glucocorticoid side effects (eg, diabetes, weight gain) and *Pneumocystis* prophylaxis are recommended. Lastly, lung transplantation may be an option for patients with severe and progressive GLILD that is not responsive to pharmacologic interventions.^{3,41}

SUMMARY

As the use of high-dose intravenous gamma globulin and available antimicrobials expands, the incidence of noninfectious CVID-related disorders, such as GLILD, is likely to increase. A thorough clinical evaluation using a multidisciplinary care model is recommended to achieve accurate diagnosis of GLILD. Enough progress has been made in the understanding of GLILD over the last decade that clinicians are now poised to conduct therapeutic trials. Data from large registries and population-based studies of GLILD are needed to better understand the disease trends and burden.

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