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## Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD): A Spectrum of Pulmonary Histopathological Lesions in Common Variable Immunodeficiency (CVID) - Histological and Immunohistochemical Analysis of 16 cases

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### Abstract

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency of unknown etiology characterized by low serum IgG, a decreased ability to make specific antibodies, and variable T cell defects. Approximately 20% of patients with CVID develop clinical evidence of a diffuse parenchymal lung disease with a constellation of histopathological findings termed granulomatous and lymphocytic interstitial lung disease (GLILD). In this study, we characterized the histological and immunohistochemical features in a series of 16 cases diagnosed by open lung biopsy. Peribronchiolar and interstitial lymphocytic infiltration, granulomatous inflammation and organizing pneumonia were consistent features; interstitial fibrosis with architectural remodeling was also found in a subgroup of patients. By immunohistochemistry, a predominance of CD4+ T lymphocytes with variable numbers of CD8+ T cells and B cells were present, with a striking absence of FOXP3 positive T regulatory cells. This heretofore unrecognized immunohistochemical finding, needs further investigation for a potential role in the pathogenesis of the condition. The presence of interstitial fibrosis with or without architectural remodeling in a subset of patients also needs additional study, for effect on prognosis.

### Keywords

Granuloma; lymphoid interstitial lung disease; common variable immunodeficiency; immunohistochemistry

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The authors contributed equally to this manuscript.

#### Disclosures:

The authors do not have any conflicts of interest.

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## 1. Introduction

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by low serum IgG, IgA and/or IgM, and poor specific antibody production. It is the most common serious primary immunodeficiency with a prevalence of 1: 25000 – 50000 [1]. In a small minority of patients, single gene mutations resulting in B and T lymphocyte dysfunction have been identified [2]. Thus, the molecular pathogenesis of the disease is not known in the vast majority of cases. Although the age of onset of symptoms is variable, the diagnosis of CVID is usually made between the second and fourth decades of life. Upper and lower respiratory tract infections are the most common presenting manifestations, occurring in a vast majority of patients [3]. In CVID, there is an undefined defect in the differentiation of B cells into mature antibody producing plasma cells that leads to hypogammaglobulinemia and poor specific antibody production. T cell abnormalities occur in up to 50% patients and likely contribute to the heterogeneous clinical manifestations of this disorder [4,5].

With introduction of high dose intravenous immunoglobulin (IVIG) or subcutaneous gammaglobulin (SCIG), the morbidity and mortality due to infection has markedly decreased [6]. In contrast, the noninfectious complications of CVID, such as autoimmunity, inflammatory bowel disease, enteropathy, hepatitis, structural lung disease, and lymphoproliferation, including B cell lymphomas have increased, occurring in nearly 70% of patients [7–9]. Many of these noninfectious complications are associated with increased mortality in CVID.

In the course of evaluating patients for the noninfectious complications of CVID, a high resolution CT scan of the chest is routinely obtained, which may demonstrate diffuse lung parenchymal disease (DLPD). The differential diagnosis of DLPD in the context of CVID is diverse and includes infection, hypersensitivity pneumonitis, cryptogenic organizing pneumonia, lymphoma and a constellation of radiological-pathological findings known as granulomatous and lymphocytic interstitial lung disease (GLILD) [1,8,9]. Although GLILD is the most common cause of DLPD in CVID, the histopathological features of this disorder are incompletely characterized. Consequently, it is frequently confused with other granulomatous lung diseases, such as sarcoidosis. A prior retrospective study of patients with GLILD found histopathologic abnormalities, including granulomata, and lymphoid hyperplasia resembling the pattern of LIP and FB [9]. While recognizing that GLILD consists of a rather heterogeneous collection of pathological findings, and that there is insufficient prospective data on the natural history of this complication of CVID, the purpose of this study was to fill a void in the available literature, by attempting a systematic characterization of the spectrum of histopathologic and immunohistochemical features of GLILD. We also endeavored to see if there were any histologic features that may potentially identify patients at increased risk for disease progression.

## 2. Materials and methods

All components of the study were performed in compliance with relevant laws and institutional guidelines, with approval from the Institutional Review Board (IRB).

## 2.1 Demographics

16 patients with the common variable immunodeficiency (CVID) constitute the study. These patients were diagnosed with CVID, using standard diagnostic criteria [10,11]. The patients [females (n=10) and males (n=6)] ranged in age from 19 – 57 years (mean age – 37) and underwent either video-assisted thoracoscopy (VATS) guided or open lung wedge biopsies.

## 2.2 Histology

Histological examinations were performed on standard 4.0 microns thick hematoxylin and eosin (H & E) stained sections of formalin-fixed, paraffin embedded specimens. The following features were assessed: (1) airway inflammation including follicular bronchitis/bronchiolitis and interstitial inflammation/lymphoid interstitial pneumonia, (2) epithelioid cell granulomata including their frequency, distribution and appearance, (3) organizing pneumonia, characterized by Masson bodies (spherical proliferations of fibroblastic tissue set in a pale, myxoid stroma located within airspaces and adjacent interstitium), (4) interstitial fibrosis, and (5) alveolar remodeling characterized by microscopic honeycomb cysts lined with metaplastic bronchiolar epithelium and traction bronchiectasis. The pathologic features were evaluated by low power examination of several representative slides from each case. Assessment of these features was done semiquantitatively using the following scores: absent (0), mild (1+), moderate (2+) and severe (3+). The histologic grading was performed by two pathologists (NR and ACM) independently and subsequently in tandem with consensus achieved. Special stains for microorganisms (Ziehl-Neelsen stain for acid fast bacilli; and Gomori Methenamine stain for fungal organisms) were performed on all cases using established staining protocols.

## 2.3 Immunohistochemistry

Paraffin blocks for immunohistochemical studies were available in all cases. Four micron sections were stained using a Dako Autostainer Plus according to the manufacturer's protocol. Slides were dried at 60°C for one hour and deparaffinized. Heat induced epitope retrieval was performed with Dako Envision FLEX target retrieval solution (high pH Tris/EDTA) at 100°C for 20 minutes. Primary antibodies (DAKO, Carpinteria, California) for: CD3 (Rabbit polyclonal), CD4 (4B12), CD8 (C8/144B), CD19 (LE-CD19), CD20 (L26), CD138 (MI15), and PAX5 (DAK-Pax5) were obtained from DAKO, Carpinteria, California. FoxP3 (236A-E7) was obtained from Abcam, Cambridge, Massachusetts. All antibodies were incubated at room temperature for 60 minutes. Signals were detected using a Dako FLEX detection kit. Counterstaining was performed with Envision FLEX hematoxylin for 7 minutes at room temperature. Appropriate positive and negative controls were run concurrently for all antibodies tested.

## 2.4 Immunohistochemical Analysis

Cytoplasmic and membranous expression of immunohistochemical staining was quantified for each case using an Automated Cellular Imaging System III (ACIS III, DAKO) as previously described [12]. For each CVID patient, a portion of lung was quantitatively analyzed by scanning a representative whole slide for each patient. ACIS software collects individual, overlapping images at 400X and then tiles these images to create a montage of

the entire scanned lung specimen. The software evaluates each individual 400X image and combines the results into an aggregate quantitative measurement corresponding to the entire tissue specimen. The ACIS system measures the intensity of the staining based on three related color parameters: the color defined by hue, the “darkness” defined as luminosity, and the density of the color defined as saturation. ACIS software for the analysis was programmed by an experienced user-pathologist (ACM) by setting the color-specific thresholds to determine and calculate staining intensity and the ratio of positively stained cells to the entire area of selection. This was used to determine the approximately percentage of positive staining tissue in each specimen.

### 3. Results

#### 3.1 Histopathology of GLILD

The histologic findings are summarized in Table 1. Nodular peribronchiolar inflammation, consisting of mature appearing lymphocytes predominantly was present in all cases (100%) (Fig A). The extent of peribronchiolar inflammation ranged from mild (1+) in 4/16 cases (25%), moderate (2+) in 9/16 cases (56 %), to severe (3+) in 3/16 cases (19%). Dense nodular and diffuse interstitial chronic was present in all 16 cases as well (Fig B). The intensity of interstitial chronic inflammation ranged from mild (1+) in 3/16 cases (19 %), moderate (2+) in 4/16 cases (25%) to severe (3+) in 9/16 cases (56 %). In cases with marked (3+) interstitial inflammatory infiltrate, there was homogeneous and uniform expansion of the interstitium by the chronic inflammatory infiltrate. Marked peribronchiolar and interstitial chronic inflammation (2+ or 3+) was present in 10/16 cases (62.5 %). It was unusual to see an isolated peribronchiolar or interstitial pattern, for example 3/16 cases (18.75 %) demonstrated significant interstitial inflammation without accompanying peribronchiolar infiltrate, whereas 2/16 cases (12.5%) showed the reverse pattern of inflammation. In one case (6.25%), there was a paucity of an inflammatory component, and neither patterns were observed in significant amounts. This case had rather advanced interstitial fibrosis with evidence of remodeling (case #3).

Granulomata, ranging from well to poorly formed, were present in 15/16 cases (93.75 %). In some areas, poorly formed granulomas were associated closely with diffuse interstitial inflammation. The granulomas were nonnecrotizing and comprised of epithelioid histiocytes with occasional multinucleate giant cells (Fig C). They were randomly distributed throughout the lung parenchyma, both in association with the lymphocytic infiltration, as well as away from the inflammatory infiltrate. They were seen within the interstitium, along bronchovascular bundles, and occasionally within alveolar spaces. The frequency of granulomata ranged from mild (1+) in 8/16 cases (50 %), moderate (2+) in 5/16 cases (31.25%), and severe (3+) in 2/16 cases (12.5%). AFB and GMS stains were negative for microorganisms in all cases.

Organizing pneumonia was present in 14/16 cases (87.5%) and characterized by Masson bodies composed of focal spherical proliferations of fibroblastic tissue set in a pale, myxoid stroma located within alveoli and adjacent interstitium (Fig D). Organizing pneumonia was mild (1+) in 7/16 cases (43.75 %), moderate (2+) in 6/16 cases (37.5 %), and severe (3+) in

1/16 cases (6.25%). In some areas, the organizing pneumonia was intimately associated with granulomas.

Interstitial fibrosis, characterized by patchy to expansive areas of collagenized fibrosis, was present in 12/16 cases (75%). It was mild (1+) in 5/16 cases (31.25%), moderate (2+) in 4/16 cases (25%), and severe (3+) in 3/16 cases (18.75%). Five of the seven cases with significant interstitial fibrosis (2+ or 3+) displayed significant accompanying alveolar remodeling characterized by irregularly shaped air spaces (microscopic honeycomb cysts) lined by metaplastic bronchiolar epithelium and associated traction bronchiectasis (Fig E). Alveolar remodeling always accompanied significant interstitial fibrosis (2+ or 3+). In other cases mild (1+) interstitial fibrosis unaccompanied by alveolar remodeling was observed.

### 3.2 Immunohistochemical analysis

Characterization of the inflammatory infiltrate by immunohistochemistry (IHC) demonstrated T cells in all cases and B cells in 15/16 cases. CD3+ CD4+ T cells were the predominant lymphocyte in all but 2 cases, where CD20+ B cells predominated (Table 2). Strikingly, regulatory T cells, characterized by nuclear FoxP3 expression, were not found in the lungs of any patient with GLILD. The inflammatory infiltrate in areas of FB was predominantly CD3+ (Fig G), CD4+ (Fig H) T cells, with smaller numbers of CD8+ T cells (Fig I), and CD20+ (Fig J), PAX5+ (Fig K) B cells. In one case of FB, a small nodule of CD20+ cells was identified. Similar nodules were more commonly observed in the interstitium and demonstrated a positive correlation with the extent of interstitial inflammation. These nodules ranged from poorly formed and few in numbers to well-formed and rather more frequent. The nodules were typically composed of CD20+, PAX5+ positive B cells cuffed by a small ring of CD3+, CD4+ cells. Cases with alveolar remodeling demonstrated strong CD138 staining within the epithelium.

## 4. Discussion

GLILD is the pulmonary component of multisystemic lymphoproliferative disease in CVID, which includes diffuse adenopathy, splenomegaly, and granulomatous inflammation in a variety of organs. It is the most common cause of DLPD in patients with CVID, occurring in approximately 10–30% of all patients [8,9,13–16]. Prior retrospective studies have suggested that the presence of GLILD in CVID is associated with increased mortality, although granulomatous disease per se in any organ may not be associated with poorer outcome [8,9,17].

Lymphoid proliferation is a cardinal manifestation of GLILD [8,9,17]. Our series highlights peribronchiolar and interstitial lymphoid infiltration as the predominant histologic patterns of lymphoid proliferation. A mixed inflammatory pattern, consisting of moderate to severe peribronchiolar and interstitial inflammation, was typically present. Only one case (which was characterized predominantly by interstitial fibrosis) demonstrated a minor/insignificant inflammatory component. Prior to the current study, there was not a quantitative analysis of the lymphocyte subtypes present in GLILD. By immunohistochemistry and the use of an Automated Cellular Imaging System we demonstrated that the lymphoid infiltrate typically had a predominance of CD4+ T cells, both in areas of FB and LIP. Nodules of CD20+ B

cells ringed by CD4+T cells were also noted, mainly within the interstitium. With the exception of one patient, all of our cases showed the presence of B cells in the affected lungs. Detailed analysis of pulmonary lymphoid populations in CVID patients with lymphoid hyperplasia has shown the presence of distinct B-cell follicles and T-cell zones, which resembles the findings in our cases [18]. This feature has been termed “tertiary lymphoid neogenesis” and has been suggested to occur in various chronic inflammatory states, including those affecting the lung.

The importance of recognizing discrete B and T cell lymphoid populations in these situations lies in the implications for treatment. Combination immunosuppressive therapy targeting both B cells (rituximab) and T cells (azathioprine) has been successfully employed in the treatment of GLILD [13]. The patient without the presence of B cells in the lung biopsy also lacked B cells in the peripheral blood. Interestingly, 8 years previous to the current lung biopsy, she had B cells both in the periphery and in the lung biopsy. The lack of B cells was clinically relevant as rituximab therapy in this case would have been an ineffective and unnecessary medication. Follow-up of this patient indicates that the pulmonary disease is stable on mycophenolate treatment. This case illustrates the utility of obtaining a repeat open lung biopsy to confirm the histological findings and diagnosis when the prior biopsy is several years in the past. It also emphasizes the importance of immunohistochemical characterization of the lymphoid infiltrate for planning treatment regimen in these patients.

Another novel immunohistochemical finding of the current study was the striking absence of regulatory T cells in the lungs in our cases with GLILD. Prior studies indicated that there is a decrease in the number and function of regulatory T cells in the peripheral blood in CVID compared to age and sex matched healthy controls [19–22]. Low numbers of regulatory T cells in the peripheral blood correlates with autoimmunity and granulomatous disease, including granulomatous lung disease, in patients with CVID [19–22]. Azathioprine and rituximab, which are used to treat GLILD, have been shown to increase the numbers of regulatory T cells [23,24]. We therefore hypothesize that the lack of regulatory T cells in the lungs of patients with GLILD is a contributing factor in the underlying pathogenesis of this disorder. To our knowledge, this is the first report describing a lack of regulatory T cells in the lung lesions of patients with GLILD.

Organizing pneumonia, in some cases a prominent histological feature, was present in a vast majority of our cases of GLILD. This finding has not been previously emphasized in GLILD. It is important to recognize that idiopathic or cryptogenic organizing pneumonia (COP) is also a common cause of DLPD in CVID patients [9,25,26]. Limited bronchoscopic lung biopsies in GLILD patients, where organizing pneumonia may be the predominant histological abnormality, may result in a mistaken diagnosis of COP. This was exemplified in one of our cases (patient #16), where a diagnosis of COP was made based on transbronchial biopsy findings. This led to the use of high dose corticosteroid therapy, which failed to result in radiographic improvement of the DLPD. A subsequent VATS biopsy established the diagnosis of GLILD, with resolution of pulmonary findings with rituximab and azathioprine therapy. The case emphasizes the importance of suggesting the diagnosis of



GLILD on open lung or VATS biopsy whenever it can safely be performed, to avoid sampling error and incorrect characterization of DLDP in these patients.

Interstitial fibrosis is also a previously unappreciated feature that is present in many patients with GLILD. Overall, 12/17 patients had interstitial fibrosis, and in 7 of these patients the fibrosis was severe. In examining the presence of interstitial fibrosis in our cases, we evaluated its extent and distribution, as well as the presence or absence of architectural remodeling including microscopic honeycombing and traction bronchiectasis. A majority of our patients with severe interstitial fibrosis (5/7) also had architectural remodeling. The presence of interstitial fibrosis in a proportion of patients with GLILD is of interest. It emphasizes the need for prospective clinical studies, lacking thus far, to address the possibility that it may be a marker for disease progression, and perhaps provide a rationale for early diagnosis and treatment.

The histologic differential diagnosis of GLILD includes a group of interstitial lung diseases displaying granulomatous, inflammatory and fibrotic features in varying proportions. The various entities and their histologic differential diagnostic features are listed in Table 3. The granulomatous process raises the possibility of both sarcoidosis and hypersensitivity pneumonitis (HP) [14,27,28]. Chronic HP can be particularly difficult to distinguish from those cases of GLILD with significant interstitial fibrosis [29], and the importance of clinical correlation in separating lesions of GLILD from HP cannot be overemphasized. Lymphoproliferation and interstitial fibrosis in GLILD may resemble idiopathic interstitial pneumonia patterns such as LIP, NSIP and UIP [30–34]. LIP is characterized by dense, diffuse chronic inflammatory interstitial infiltrate, and significant granulomas or organizing pneumonia are variable, but generally inconspicuous [35,36]. Fibrotic NSIP and UIP may prove difficult to distinguish from GLILD with significant interstitial fibrosis, as seen in a subset of our cases. Finally, infection should always be considered in the differential diagnosis. Granulomatous infectious processes need to be excluded by appropriate special stains and microbiological studies. In summary, distinguishing various other granulomatous, inflammatory and fibrotic interstitial lung diseases from GLILD requires a high index of suspicion and significant clinical and microbiologic correlation.

Recent studies show that pulmonary lesions similar to GLILD can also occur in primary immunodeficiencies other than CVID, for example, cytotoxic T lymphocyte antigen-4 (CTLA4) deficiency, lipopolysaccharide responsive beige-like anchor protein (LRBA) deficiency and hypomorphic mutations in the recombina-activating gene 1 (Rag1) [37–40]. Importantly, hypogammaglobulinemia may be one of the immunological abnormalities found in these primary immunodeficiencies. There are also several primary immunodeficiencies that have granulomatous inflammation in extrapulmonary locations [41]. As more patients with these rare diseases are diagnosed and additional monogenic cause of primary immunodeficiencies are described, we believe that the number of primary immunodeficiencies where GLILD is found will increase.

## 5. Conclusions

In summary, GLILD is a conglomeration of pulmonary histopathological abnormalities seen in a subset of patients with CVID. Recent descriptions of similar findings in patients with other immune abnormalities, emphasizes that GLILD may represent a pulmonary reaction pattern that serves as a morphological endpoint in patients with these uncommon conditions. Granulomas, peribronchiolar and interstitial lymphocytic infiltration are present in nearly all patients with GLILD. Extensive organizing pneumonia and pulmonary interstitial fibrosis are also seen in a significant proportion of patients with GLILD. T cells, particular CD4+ T cells, are the predominant lymphocytes in the lung, with B cells present to a lesser extent. B cell predominance is seen in a minority of cases of GLILD. We also observed a near total absence of regulatory T cells, a finding that warrants further investigation. To the best of our knowledge, our description of significant interstitial fibrosis and large areas of organizing pneumonia, quantification of lymphocytic subsets, and observation of an absence of regulatory T cells in lung biopsy specimens, are unique findings that have not been described. Finally, our findings emphasize that GLILD is best assessed on open lung or VATS biopsies, rather than limited transbronchial biopsies.

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### GLILD Highlights for Review

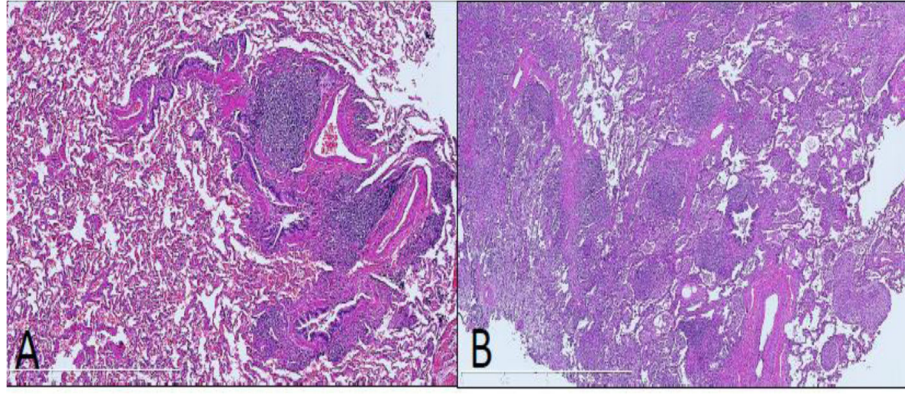
This study characterizes histological and immunohistochemical findings in GLILD in patients with COVID.

FB, LIP, granulomatous inflammation and organizing pneumonia were consistent findings.

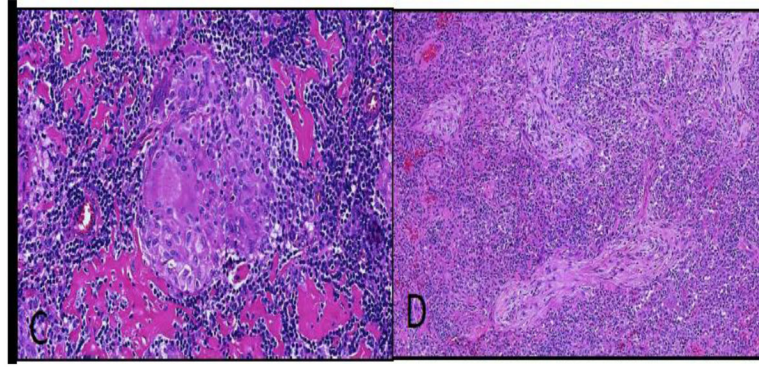
Organizing pneumonia may be the dominant feature and has potential for misdiagnosis on limited transbronchial biopsies.

Interstitial fibrosis, previously not emphasized, can be present in a proportion of cases, likely carries worse prognosis and requires additional study.

We demonstrate predominance of CD4+ T cells, and hithertofore unreported striking absence of FOXP3 positive regulatory T cells, which needs investigation for a role in pathogenesis of GLILD.

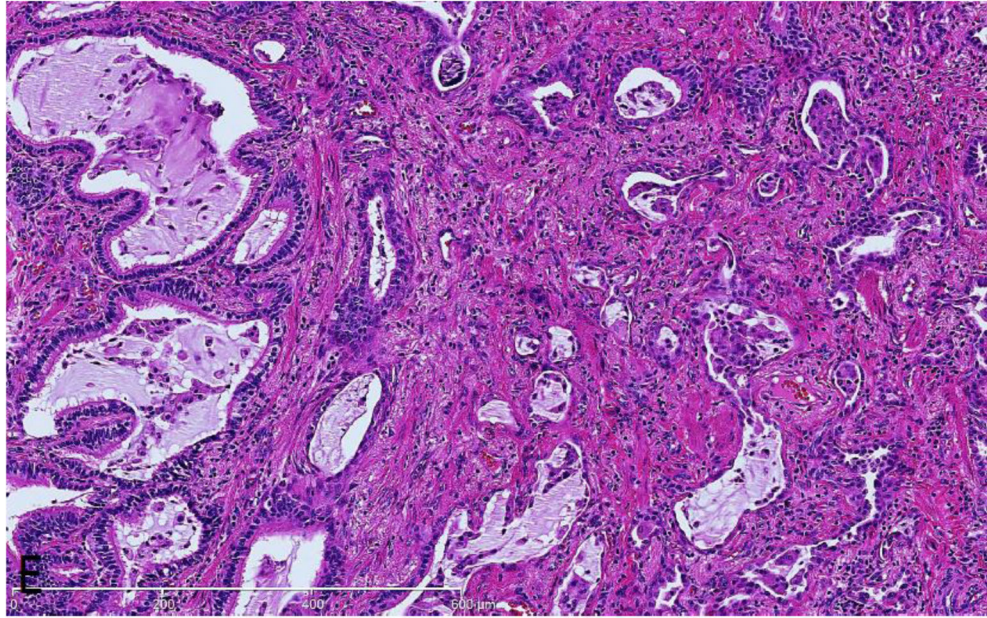


**Figure A, B.** Peribronchiolar and interstitial lymphocytic infiltration in GLILD. There are nodular lymphoid aggregates associated with bronchioles (A), and dense, nodular and diffuse interstitial lymphocytic infiltration (B). (H&E, 100x)



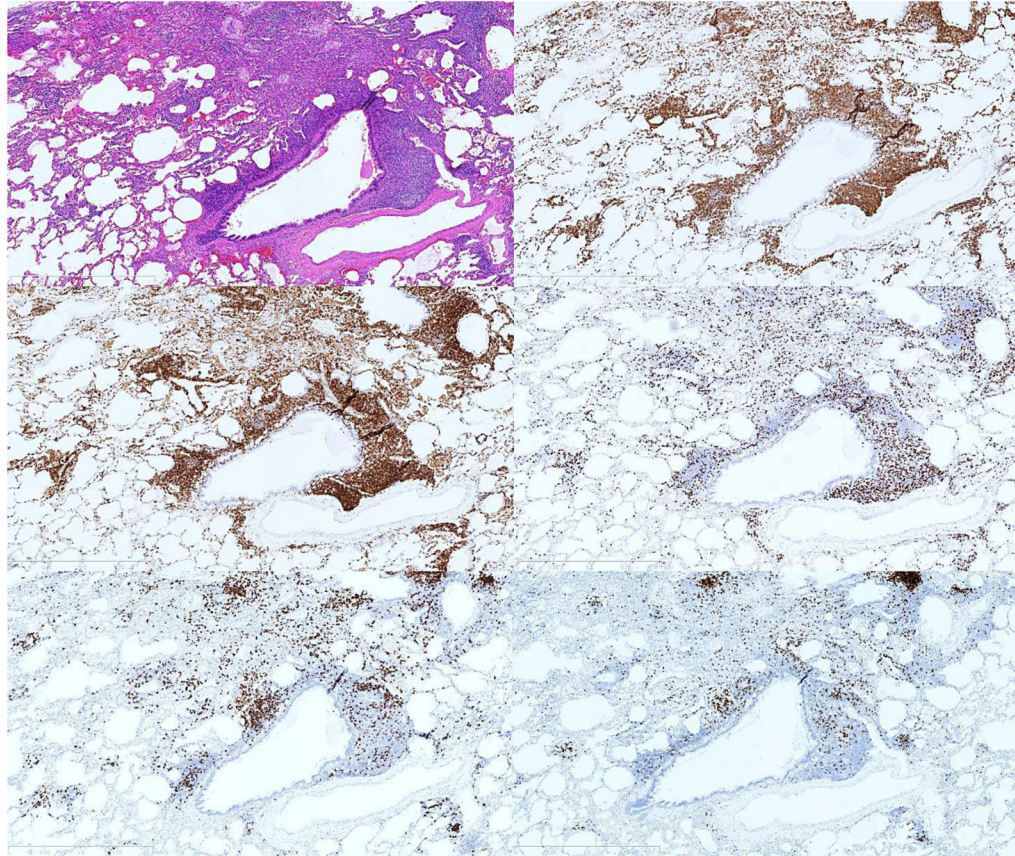
**Figure C, D.** Granulomata and organizing pneumonia in GLILD. A well-formed epithelioid cell granuloma (C), and organizing pneumonia characterized by prominent Masson bodies within airspaces (D). (H&E, 200x (C), 100x (D))





**Figure E.**  
Interstitial fibrosis in GLILD. There is expansile interstitial fibrosis with remodeled airspaces lined by metaplastic bronchiolar epithelium. (H&E, 200x)





**Figure F-K.**

T lymphocyte predominance in GLILD. FB pattern infiltrate in GLILD (F) with predominantly CD3 positive (G), CD4 positive T cells (H), with smaller numbers of CD8 positive T cells (I) and CD20 positive (J), PAX-5 positive B cells (K). This pattern of T lymphocyte predominance was commonly observed.

**Table 1**

**Histologic Features of GLILD**

	Patient Age/Sex	Inflammation		Granulomas	Organizing Pneumonia	Fibrosis	
		Bronchiolar	Interstitial			Interstitial Fibrosis	Remodeling
1.	19/F	3	1	1	0	0	0
2.	24/F	3	3	1	2	1	0
3.	53/F	1	1	1	0	2	2
4.	49/F	2	3	3	1	3	2
5.	49/M	1	2	2	1	3	2
6.	30/M	2	3	2	3	1	0
7.	28/F	1	3	2	2	0	0
8.	30/F	2	3	0	2	1	0
9.	49/M	2	3	1	1	2	2
10.	57/M	1	2	1	1	3	1
11.	39/F	2	3	3	2	2	0
12.	35/F	3	2	2	2	0	0
13.	34/M	2	2	2	1	1	0
14.	43/M	2	1	1	1	0	0
15.	33/F	2	3	1	1	2	2
16.	27/F	2	3	1	2	1	0

**Table 2**

Ratio of lymphocyte subtypes by immunohistochemical staining in GLILD

Pt	CD4/CD3	CD8/CD3	CD4/CD8	FOXP3/CD3	CD138/PAX5	CD3/CD20+CD3	CD138/CD20	PAX5/CD20	CD3/CD20
1	1.04	0.52	2.01	0.03	0.49	0.59	0.27	0.54	1.44
2	1.03	0.37	2.79	0.02	0.77	0.61	0.39	0.51	1.58
3	0.81	0.6	1.36	0.07	6.39	0.92	3.84	0.6	10.84
4	0.98	0.55	1.78	0	0.06	0.58	0.04	0.56	1.35
5	0.82	0.59	1.38	0.02	2.27	0.77	0.71	0.31	3.33
6	0.86	0.25	3.52	0.02	2.7	0.85	0.58	0.21	5.5
7	1.02	0.4	2.53	0.01	NA	0.45	NA	0.58	0.8
8	0.31	0.29	1.07	0.01	NA	0.4	NA	0.56	0.68
9	0.78	0.63	1.24	0.03	0.1	0.44	0.06	0.65	0.79
10	1.28	0.53	2.43	0.03	95.57	0.99	127.49	1.33	149.15
11	1.42	0.14	10.14	NA	NA	0.68	NA	NA	2.08
12	0.63	0.12	5.3	NA	NA	0.82	NA	NA	4.55
13	NA	NA	NA	NA	NA	NA	NA	NA	NA
14	1.62	0.37	4.44	NA	NA	0.68	NA	NA	2.11
15	1.96	0.26	7.48	NA	NA	0.52	NA	NA	1.07
16	2.69	2.25	1.2	NA	NA	0.56	NA	NA	1.29
<b>Median</b>	<b>1.02</b>	<b>0.4</b>	<b>2.43</b>	<b>0.02</b>	<b>1.52</b>	<b>0.61</b>	<b>0.485</b>	<b>0.56</b>	<b>1.58</b>
<b>Average</b>	<b>0.92</b>	<b>0.42</b>	<b>2.96</b>	<b>0.02</b>	<b>13.55</b>	<b>0.67</b>	<b>16.67</b>	<b>0.59</b>	<b>15.18</b>
<b>Standard Deviation</b>	0.59	0.5	2.62	0.02	33.21	0.18	44.79	0.3	37.91

NA: Analysis not performed.

**Table 3**

## Entities and Patterns In The Histologic Differential Diagnosis of GLILD

	Microscopic features			
<b>GLILD</b>	Well, moderate or poorly circumscribed; May be cuffed by lymphocytes or associated with lymphoid infiltration; random distribution	Lymphocytic infiltration of variable density – peribronchiolar and interstitial	Consistently present; associated with interstitial inflammation	Present in a subset of patients; expansile and associated with interstitial inflammation
<b>Sarcoidosis</b>	Well circumscribed; “naked” – unassociated with lymphocytic cuffing; lymphatic distribution	Significant interstitial inflammation is absent	Usually absent	Present in a subset of patients; with a distribution similar to granulomatous inflammation
<b>Hypersensitivity pneumonitis</b>	Well, moderate or poorly circumscribed; May be cuffed by lymphocytes or associated with lymphoid infiltration; bronchiolocentric or random distribution	Bronchiolocentric or diffuse interstitial chronic inflammation	Present, associated with peribronchiolar or interstitial inflammation and granulomas	May be present in chronic HP; and may follow a pattern similar to UIP
<b>Lymphoid interstitial pneumonia</b>	Granulomas are usually absent; isolated multinucleate giant cells with cholesterol clefts may be present	Diffuse interstitial chronic inflammatory infiltrate, with lymphoid aggregate formation	May be present focally (minor feature)	Usually absent
<b>Nonspecific interstitial pneumonia</b>	Granulomas are usually absent; isolated multinucleate giant cells with cholesterol clefts may be present	Homogeneous interstitial expansion by a variable intensity chronic inflammatory infiltrate	May be present focally (minor feature)	May be present in fibrosing NSIP; fibrosis follows a homogeneous and diffuse pattern similar to interstitial inflammation in cellular NSIP
<b>Usual interstitial pneumonia</b>	Granulomas are usually absent; isolated multinucleate giant cells with cholesterol clefts may be present	Scant and patchy chronic interstitial inflammation	Usually absent (if present; may raise the possibility of acute exacerbation of UIP)	Characteristic feature; patchwork fibrosis which is temporally heterogeneous (coexistent “young and old” fibrosis)

GLILD – Granulomatous and Lymphocytic Interstitial Lung Disease

HP – Hypersensitivity Pneumonitis

NSIP – Nonspecific Interstitial Pneumonia

UIP – Usual Interstitial Pneumonia