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Original contribution

# Granulomatous and lymphocytic interstitial lung disease: a spectrum of pulmonary histopathologic lesions in common variable immunodeficiency—histologic and immunohistochemical analyses of 16 cases☆,☆☆

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**Summary** Common variable immunodeficiency is a primary immunodeficiency of unknown etiology characterized by low serum immunoglobulin G, a decreased ability to make specific antibodies, and variable T-cell defects. Approximately 10-30% of patients with common variable immunodeficiency develop clinical evidence of a diffuse parenchymal lung disease with a constellation of histopathologic findings termed *granulomatous and lymphocytic interstitial lung disease*. In this study, we characterized the histologic 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 was 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.


## 1. Introduction

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by low serum immunoglobulins G, A, and/or M and poor specific antibody production. It is the most common serious primary immunodeficiency with a prevalence of 1:25 000 to 50 000 [1]. In a small minority of patients, single gene mutations resulting in B- and T-lymphocyte dysfunction have been identified [2].

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Thus, the molecular pathogenesis of the disease is not known in most 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 most 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 or subcutaneous gammaglobulin, the morbidity and mortality due to infection have 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 computed tomographic 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 (HP), cryptogenic organizing pneumonia, lymphoma, and a constellation of radiologic-pathologic 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 histopathologic 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 lymphoid interstitial pneumonia (LIP) and follicular bronchiolitis (FB) [9]. Although recognizing that GLILD consists of a rather heterogeneous collection of pathologic findings and that there are 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.

### 2.1. Demographics

Sixteen patients with 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 to 57 years (mean age, 37 years) and underwent either video-assisted thoracoscopy (VATS)–guided or open lung wedge biopsy.

### 2.2. Histology

Histologic examinations were performed on standard 4.0-$\mu$m-thick hematoxylin and eosin (H&E)–stained sections of formalin-fixed, paraffin-embedded specimens. The following features were assessed: (1) airway inflammation including FB/bronchiolitis and interstitial inflammation/LIP; (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 2 pathologists (N. R. and A. C. M.) independently and subsequently in tandem with consensus achieved. Special stains for microorganisms (Ziehl-Neelsen stain for acid-fast bacilli and Gomori methenamine-silver 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-micrometer sections were stained using a Dako Autostainer Plus (Carpinteria, CA) according to the manufacturer's protocol. Slides were dried at 60°C for 1 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) for CD3 (rabbit polyclonal), CD4 (4B12), CD8 (C8/144B), CD19 (LE-CD19), CD20 (L26), CD138 (MI15), and PAX5 (DAK-Pax5) were obtained from Dako. FoxP3 (236A-E7) was obtained from Abcam (Cambridge, MA). 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.