



Contents lists available at ScienceDirect



Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations

Paul J. Maglione, MD, PhD^{*,†}; Jessica R. Overbey, MS[†]; Lin Radigan, BMed^{*,‡}; Emilia Bagiella, PhD[†]; and Charlotte Cunningham-Rundles, MD, PhD^{*,‡}

^{*} Department of Medicine, Division of Clinical Immunology, Icahn School of Medicine at Mount Sinai, New York, New York

[†] Department of Health Evidence and Policy, Icahn School of Medicine at Mount Sinai, New York, New York

[‡] Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, New York

ARTICLE INFO

Article history:

Received for publication March 6, 2014.

Received in revised form April 8, 2014.

Accepted for publication April 29, 2014.

ABSTRACT

Background: It remains unclear whether interstitial lung disease (ILD) in common variable immunodeficiency (CVID) is a consequence of chronic infection or a manifestation of dysregulated lymphoid proliferation found in those with this condition.

Objective: To increase understanding of CVID-associated lung disease by comparing clinical and immunologic associations in those with bronchiectasis, ILD, or no lung disease observed on chest computerized tomography (CT).

Methods: Retrospective review of electronic medical records of 61 patients with CVID was used to identify clinical and laboratory correlates of bronchiectasis, ground glass opacity, and pulmonary nodules on CT scan.

Results: Significant clinical and immunologic associations were identified for common CT scan findings in CVID. Bronchiectasis was strongly correlated with a CD4⁺ T-cell count lower than 700 cells/ μ L and was associated with a history of pneumonia and older age. Pulmonary nodular disease was correlated with increased CD4⁺:CD8⁺ T-cell ratios, a history of autoimmune hemolytic anemia or immune thrombocytopenic purpura, elevated IgM, and younger age. Ground glass opacity had similar clinical and laboratory characteristics as those for nodular lung disease but was associated with elevated monocyte counts and the presence of liver disease.

Conclusion: CT findings of bronchiectasis or ILD, including ground glass opacity and extensive pulmonary nodules, were correlated with selected clinical and laboratory characteristics. These results suggest divergent processes of CVID lung disease, with bronchiectasis more strongly associated with infection and T-cell lymphopenia and ILD more strongly linked with autoimmunity and lymphoproliferation.

© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency¹ and is characterized by predisposition to sinopulmonary infections and susceptibility to noninfectious complications such as autoimmunity and malignancy.² Chronic lung disease is among the most common complications of CVID, affecting 29% to 58% of patients, depending on the study population.^{3–5} Ten years previously, it was established by Bates et al⁶ that interstitial lung disease (ILD) significantly worsens

survival in CVID. However, established CVID lung disease has proved difficult to treat and is not reversed by conventional immunoglobulin replacement therapy in most patients,⁷ although it may improve pulmonary function testing.^{8,9}

Radiologic evaluation of lungs in CVID discloses different chronic pulmonary findings, including air trapping, bronchial wall thickening, bronchiectasis, emphysema, ground glass opacities, parenchymal consolidation, pulmonary nodules, and/or scarring or fibrosis.^{7,10–12} Lung pathology may show ILD with manifestations of pulmonary lymphoid hyperplasia (PLH), which includes follicular bronchiolitis, lymphocytic interstitial pneumonitis (LIP), and nodular lymphoid hyperplasia.^{6,13–15} In addition, granulomatous lung disease is found in many cases^{16–18} and organizing pneumonia (OP) in some.^{19–21} Granulomatous-lymphocytic interstitial lung disease has been used as an encompassing term for this combination of pathologic findings in CVID.⁵

The pathogenesis of lung disease in CVID is not well understood. Although as many as 50% of patients with CVID reportedly develop

Reprints: Charlotte Cunningham-Rundles, MD, PhD, Departments of Medicine and Pediatrics, The Immunology Institute, Mount Sinai School of Medicine, 1425 Madison Avenue, New York, NY 10029; E-mail: Charlotte.Cunningham-Rundles@mssm.edu.

Disclosures: Authors have nothing to disclose.

Funding: Supported by the Thrasher Research Fund Early Career Award, Baxter-Clinical Immunology Society Senior Fellowship Award, Jeffrey Modell Foundation, National Institutes of Health grants AI 048693 and AI 061093, and the David S. Gottesman Immunology Chair.

Table 1
Patient characteristics

Patient characteristics (n = 61)	
Age (y), range (median)	14–89 (47)
Women, n (%)	34 (56)
Medical complications, n patients (%)	
History of pneumonia	33 (54)
Splenomegaly/splenectomy	27 (44)
AIHA/ITP	23 (38)
Liver disease	8 (13)
Enteropathy	6 (10)
Laboratory characteristics, range (median)/normal reference range	
Diagnostic IgG (mg/dL)	8–400 (169)/600–1,600
Therapeutic IgG (mg/dL)	307.4–1,312 (806.3)/600–1,600
IgA (mg/dL)	2–78.3 (5)/70–400
IgM (mg/dL)	0–243 (12.9)/40–230

Abbreviations: AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura.

bronchiectasis, not all have or progress to ILD.¹¹ Development of lung disease in patients with CVID has been associated with a low CD4⁺:CD8⁺ T-cell ratio in bronchoalveolar lavage,²² decreases in

peripheral CD8⁺ T cells,⁶ and fewer numbers of IgM-IgD-CD27⁺ isotype-switched and IgM⁺CD27⁺ memory B cells^{23,24} in some, but not all, studies.²⁵ Epstein-Barr virus may be associated with PLH,²⁶ as in patients with human immunodeficiency virus,²⁷ but Epstein-Barr virus has not been found in lung biopsies from patients with CVID and PLH.¹³ Similarly, human herpesvirus-8 was associated with granulomatous-lymphocytic interstitial lung disease in 1 study,²⁸ although this has not been confirmed. Noninfectious pathogenic mechanisms for the development of CVID lung disease also have been proposed, including aberrant B-cell lymphoproliferation²⁹ and T-cell–driven autoimmunity.¹⁴ Through retrospective chart review, the authors found bronchiectasis to be associated with a history of pneumonia and decreased CD4⁺ T cells in CVID. In contrast, patients with computed tomographic (CT) evidence of ILD shared clinical and radiologic characteristics that differed from those with bronchiectasis alone or no chest CT findings. In addition, the presence of numerous pulmonary nodules was linked to autoimmunity, elevation of IgM, and increased CD4⁺:CD8⁺ T-cell ratio, whereas progression to ground glass opacity was associated with elevated peripheral monocytes and increased prevalence of liver disease.

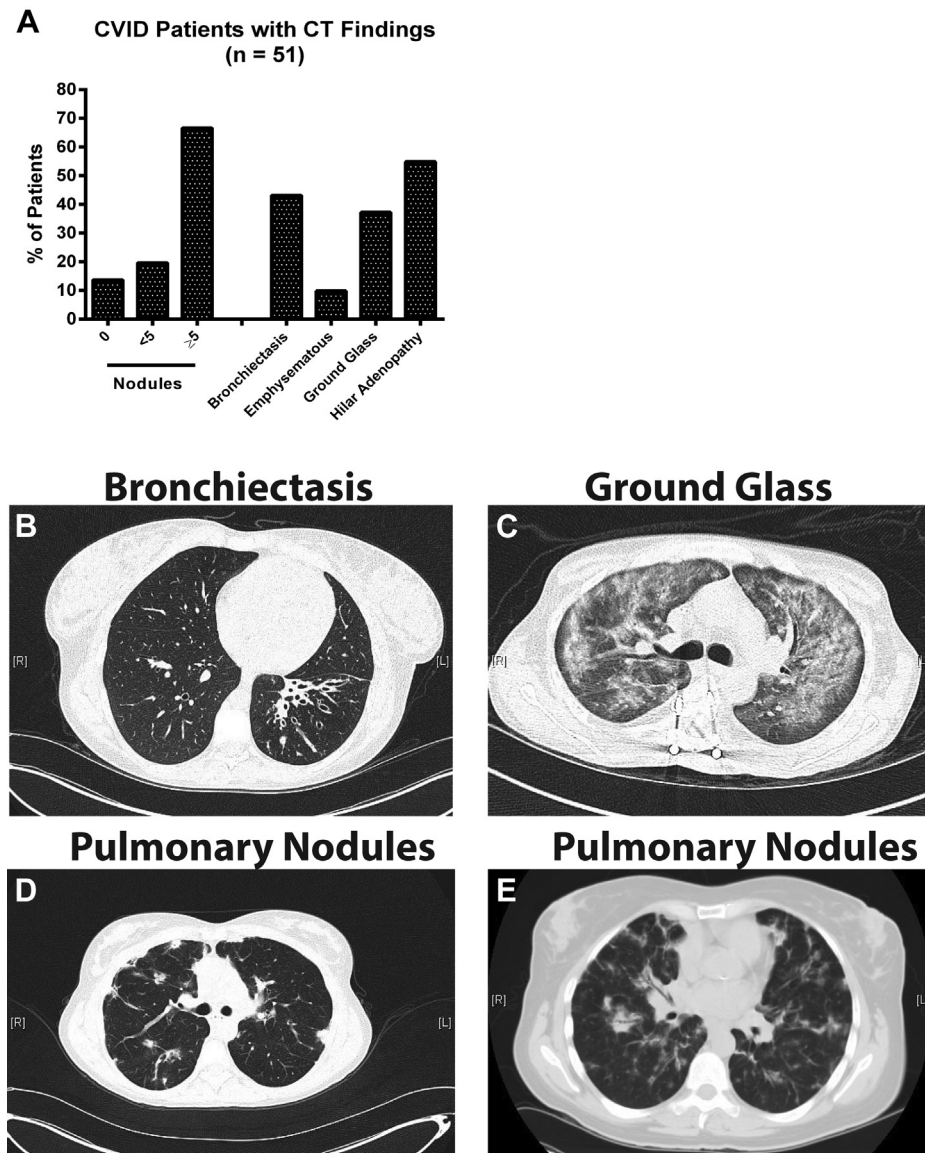


Figure 1. Chest computed tomography (CT) in common variable immunodeficiency (CVID). (A) Overall findings. (B) Left lobe bronchiectasis and bronchial wall thickening. (C) Diffuse ground glass. (D) Bilateral nodules and bronchiectasis. (E) Nodules with ground glass.

Table 2
Associations of clinical and radiologic characteristics

	Ground glass opacity ^a	≥5 Pulmonary nodules ^a	Bronchiectasis only	No lung disease ^b
Patients, n	18	34	9	13
Women, n (%)	20 (56)	20 (59)	5 (56)	7 (54)
Age (y), median (≥50 y old)	44 (33)	45 (35)	60 (67)	43 (39)
Patients, n (%), with				
Ground glass ≥1 Nodule	18 (100)	13 (38)	0 (0)	0 (0)
Bronchiectasis	16 (89)	34 (100)	4 (44)	3 (23)
Hilar adenopathy	6 (33)	12 (35)	9 (100)	0 (0)
History of pneumonia	11 (61)	24 (71)	3 (33)	0 (0)
Splenomegaly/splenectomy	8 (44)	21 (62)	7 (78)	7 (54)
AIHA/ITP	10 (56)	24 (71)	1 (11)	1 (8)
Liver disease	9 (50)	21 (62)	0 (0)	1 (8)
Enteropathy	5 (28)	6 (18)	0 (0)	0 (0)
	2 (11)	3 (9)	1 (11)	1 (8)
	ILD	No ILD	P value	
Patients, n	39	22		
Patients, n (%), with				
History of pneumonia	22 (56)	14 (64)	.78	
Splenomegaly/splenectomy	24 (63)	2 (9)	<.0001	
AIHA/ITP	22 (56)	1 (5)	<.0001	
Liver disease	8 (21)	0 (0)	.042	
Enteropathy	4 (10)	2 (9)	1.00	

Abbreviations: AIHA, autoimmune hemolytic anemia; ILD, interstitial lung disease; ITP, immune thrombocytopenic purpura.

^aPatients were included in the 2 groups if ground glass opacity and at least 5 pulmonary nodules were present.

^bIncludes patients with no computed tomographic findings and those with 1 to 4 pulmonary nodules but no bronchiectasis or ground glass opacity.

Methods

Study Design

This study was conducted through retrospective review of electronic medical records from Mount Sinai Hospital (New York, New York). Electronic medical records and supplemental material are available for patient encounters from January 2003 until the present. Patients with the *International Classification of Diseases, Ninth Revision* code for CVID (279.06) who had a CT scan of the chest or tissue biopsy pathology report in the medical record were selected. One hundred twenty-six patients were identified using these initial search parameters. These records were screened to confirm that the diagnostic criteria of CVID were met based on markedly low IgG and IgA and/or IgM levels (IgG ≤400 mg/dL, IgA <45 mg/dL, IgM <35 mg/dL), poor response to vaccines, and exclusion of other causes of hypogammaglobulinemia.³⁰ The study required (1) at least 1 radiology report of chest CT and (2) availability of peripheral blood leukocyte counts and quantitative immunoglobulin levels. Patients with known hematologic malignancy were excluded. Of the 126 patients identified in the initial screen, 41 were excluded because the diagnostic guidelines for CVID could not be confirmed and/or the patient had a hematologic malignancy. Of the remaining 85 patients, 21 were excluded owing to the absence of chest CT scans and 3 were excluded because laboratory results were not available. The remaining 61 patients with CVID were included in the analysis. This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai.

Data Collection

Radiology reports from all chest CT scans were reviewed, and the presence of bronchiectasis, emphysematous changes, ground glass opacities, and hilar adenopathy and the number of pulmonary nodules, if any, were recorded. If the radiology report used a term

such as “extensive” or “numerous” to signify a number of nodules that was too large to count, the patient was included in the category of at least 5 nodules. Nodules at least 1 mm were counted. Patient age, sex, and history of pneumonia, autoimmune hemolytic anemia (AIHA) or immune thrombocytopenic purpura (ITP), splenomegaly or splenectomy, liver disease (defined as the presence of alkaline phosphatase >110 U/L and abdominal imaging showing parenchymal disease), and enteropathy (based on suggestive clinical history with presence of colitis, enteritis, intraepithelial lymphocytosis, and/or villous blunting found at endoscopic biopsy examination) were derived from the medical record. The numbers of patients with obstructive (7%), restrictive (53%), and normal (40%) spirometric results are similar to previously published studies of CVID.^{17,24} The most consistent pulmonary function test result in the present cohort of patients with CVID lung disease was impaired diffusing capacity of the lung for carbon monoxide (80%), in agreement with other reports.^{13,17,31} Diffusing capacity of the lung for carbon monoxide in the present cohort ranged from 28% to 117%.

Means of up to 5 of the most recent laboratory values in the medical record were used to quantify neutrophils, monocytes, eosinophils, and serum IgG, IgA, and IgM. Treatment IgG level was determined as the average of IgG values after at least 2 years of immunoglobulin replacement therapy. Flow cytometry of at least 1 sample, and as many as 3 averaged together, was used to quantify CD19⁺ total B cells, CD3⁺ total T cells, CD3⁺CD4⁺ T-helper cells, and CD3⁺CD8⁺ cytotoxic T cells and the percentage of total B cells of IgM-IgD isotype-switched and IgM⁺CD27⁺ memory B cells.

Statistical Analysis

Associations between pathologic or radiologic findings and categorical clinical parameters were assessed by Fisher exact tests. Differences in continuous laboratory values between groups were assessed using 1-way analysis of variance. If an analysis of variance *F* test yielded a *P* value less than .05, differences between patients with a specific radiologic finding and those in other groups were assessed using the Dunnett test, which adjusts for multiple comparisons. Non-normally distributed laboratory values (diagnostic IgG, IgA, IgM, neutrophils, monocytes, natural killer cells, CD8⁺ T cells, total B cells, CD27⁺IgM⁺ B cells, and isotype-switched memory B cells) were rank-transformed before analysis.

Negative predictive value (NPV), positive predictive value (PPV), odds ratio, sensitivity, and specificity were calculated to examine the predictive utility of specific clinical and laboratory parameters within this patient cohort. For these statistical analyses, laboratory cutoff values were established at 700 CD4⁺ T cells/μL, the midpoint of the normal distribution of values within the present cohort, and 500 monocytes/μL, which was rounded from the median value in the present cohort of 460.

Results

Radiologic Studies

Of the 61 patients with CVID in this study, 34 were women and 27 were men. The age range of the patients was 14 to 89 years, with a median age of 47 years. Baseline IgG, averaged IgA, IgM, post-treatment IgG values, and medical complications are listed in Table 1. Ten of these patients did not have CT abnormalities. For the 51 patients with radiologic findings, 34 (67%) had at least 5 pulmonary nodules, 22 (43%) had bronchiectasis, and 18 (37%) had ground glass opacity (Fig 1A). For illustration, examples of chest findings are a 32-year-old woman with a history of pneumonia with severe left lobe bronchiectasis and bronchial wall thickening (Fig 1B), a 29-year-old man with extensive ground glass appearance throughout the lungs (Fig 1C), and a 52-year-old woman with splenomegaly, bilateral pulmonary nodules, bronchiectasis, and atypical lymphoid

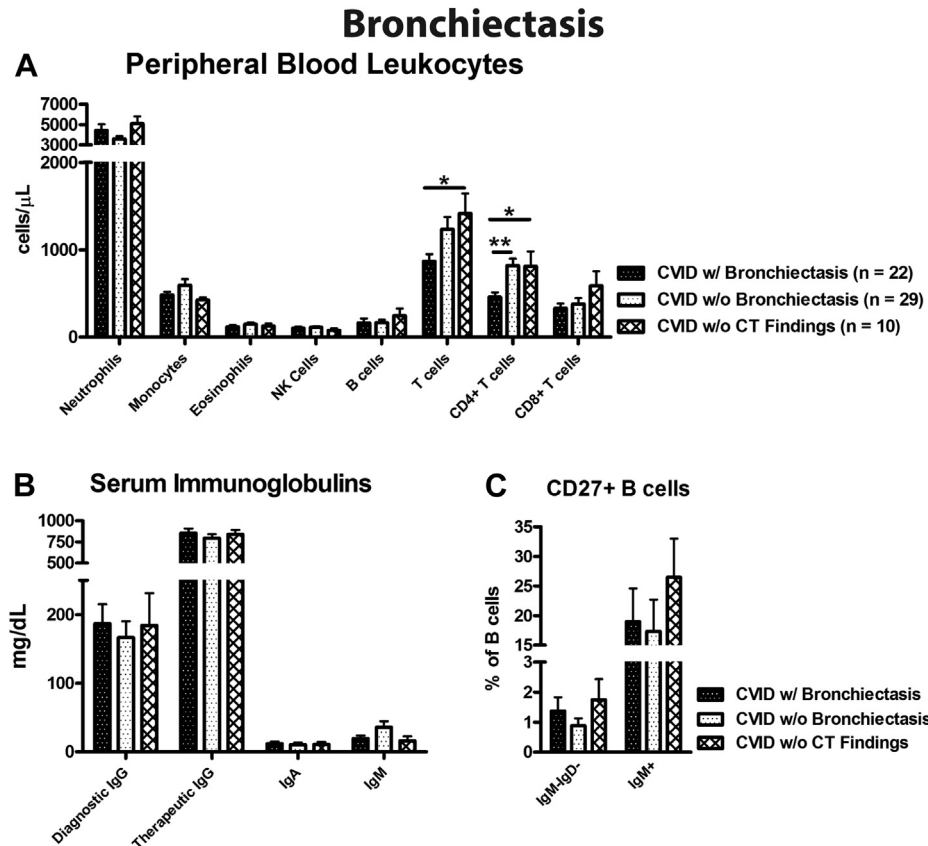


Figure 2. Laboratory associations with bronchiectasis. (A) Peripheral blood leukocytes. (B) Quantitative serum immunoglobulins. (C) CD27⁺ B-cell percentage. * $P < .05$, ** $P < .01$. CT, computed tomography; CVID, common variable immunodeficiency.

hyperplasia at lung biopsy examination (Fig 1D). Another patient was a 63-year-old woman with hepatosplenomegaly and colitis with nodular densities throughout the lungs in a somewhat peripheral pattern and ground glass changes; biopsy examination showed bronchiolocentric interstitial pneumonia with fibrosis, lymphoid hyperplasia, OP, and occasional poorly formed granulomas (Fig 1E).

Clinical and Radiologic Observations

Patients with ground glass opacity or at least 5 pulmonary nodules were younger than those with bronchiectasis but no ILD (median ages 33 and 35 vs 67 years; Table 2). The radiologic finding of bronchiectasis was not commonly observed in patients with ILD on CT scans, because only a minority of patients with ground glass opacity (33%) or at least 5 pulmonary nodules (35%) also had bronchiectasis. However, pulmonary nodules were commonly observed with ground glass opacity, because nearly

90% of patients with CVID with ground glass also had at least 1 pulmonary nodule, suggesting that these radiologic features are common aspects of ILD.^{32,33} Given the significant radiologic overlap in those with ground glass opacity and pulmonary nodules, these 39 patients were grouped together as having ILD for statistical analysis. Patients with CVID ILD were compared with the 22 patients without ILD, consisting of 10 patients with no CT findings, 9 patients with bronchiectasis only, and 3 patients with 1 to 4 pulmonary nodules but no other chest abnormalities. CVID ILD was significantly associated with splenectomy or splenomegaly ($P < .0001$), history of AIHA or ITP ($P < .0001$), and liver disease ($P < .05$). There was no significant difference between patients with and those without ILD for history of pneumonia or enteropathy. Only patients with ILD had liver disease, and those with ground glass opacity had the largest percentage of liver abnormalities (28%).

Table 3

Predictive value of clinical and laboratory parameters

CT Finding	Parameters	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	OR (95% CI)
Bronchiectasis	CD4 < 700	82% (60–95)	55% (36–73)	56% (38–74)	81% (58–94)	5.5 (1.5–20)
	CD4 < 700 and PNA Hx	62% (39–82)	74% (55–88)	62% (39–82)	74% (55–88)	4.7 (1.4–15)
	CD4 < 700 and age ≥ 50 y	50% (28–72)	90% (74–98)	79% (49–95)	72% (55–85)	9.3 (2.2–40)
≥ 5 Nodules	(1) CD4: CD8 > 2, (2) AIHA or ITP Hx, (3) IgM > 18					
	≥ 1	92% (78–98)	50% (29–71)	74% (59–86)	80% (52–95)	11 (2.7–47)
	≥ 2	63% (44–80)	93% (76–99)	91% (70–99)	69% (52–84)	22 (4.3–109)
	3	18% (7–35)	100% (87–100)	100% (54–100)	48% (34–62)	12 (0.7–225)
Ground glass	monocytes > 500	67% (41–87)	79% (64–90)	57% (34–78)	85% (70–94)	7.6 (2.2–26)
	monocytes > 500 and SMB < 0.5%	41% (19–67)	91% (77–97)	64% (30–90)	79% (65–90)	6.7 (1.6–27)

Abbreviations: CI, confidence interval; CT, computed tomographic; Hx, history; NPV, negative predictive value; OR, odds ratio; PNA pneumonia; PPV, positive predictive value; SMB, switched memory B cell.

Pulmonary Nodules

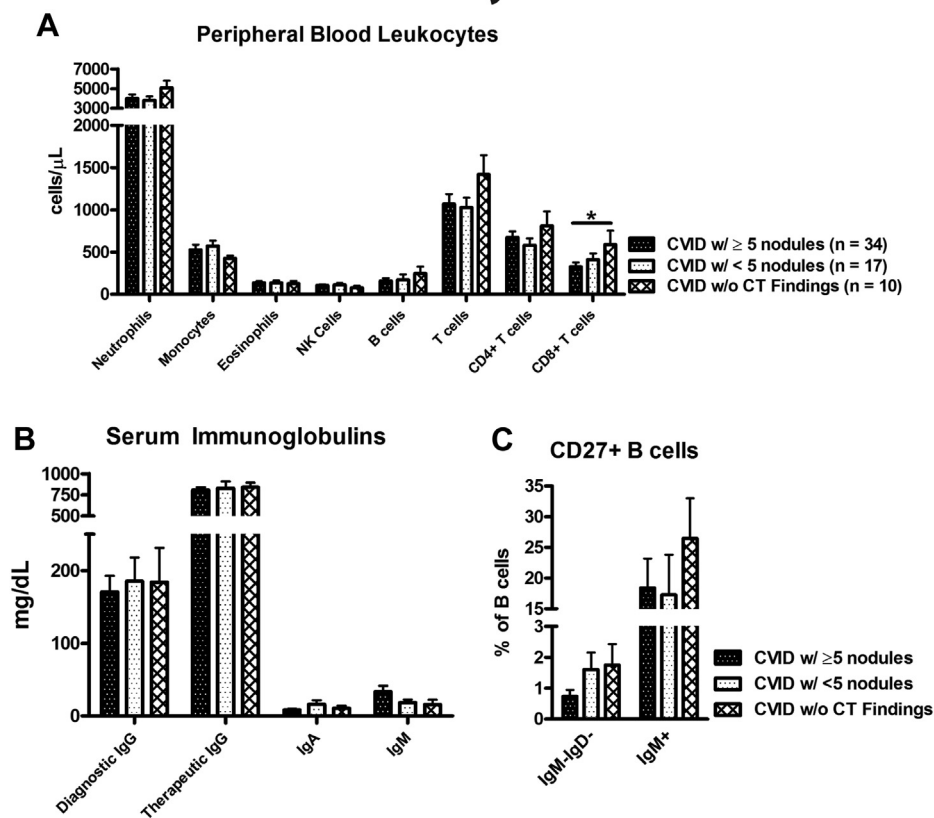


Figure 3. Laboratory associations with at least 5 pulmonary nodules. (A) Peripheral blood leukocytes. (B) Quantitative serum immunoglobulins. (C) CD27⁺ B-cell percentage. * $P < .05$. CT, computed tomography; CVID, common variable immunodeficiency.

Correlation of Clinical and Laboratory Data with Radiologic Findings

Patients with CVID and bronchiectasis had significantly fewer CD4⁺ T cells than those with CVID and other CT findings ($P < .01$) and fewer total CD3⁺ T cells and CD4⁺ T cells compared with those with no CT findings ($P < .05$; Fig 2). CD4⁺ T-cell count lower than 700 cells/ μ L had a sensitivity and NPV of approximately 80% for bronchiectasis, although only a moderate specificity (55%; Table 3). Adding an age cutoff of at least 50 years increased specificity to 90%, with a PPV of 79%. The odds of having bronchiectasis was 9 times greater for patients at least 50 years of age with CD4⁺ T-cell counts lower than 700/ μ L and 4.5 times greater for those with a history of pneumonia and CD4⁺ T-cell counts lower than 700/ μ L.

Patients with at least 5 pulmonary nodules had fewer CD8⁺ T cells ($P < .05$) but similar numbers of CD4⁺ T cells and total CD3⁺ T cells to those of patients with CVID without CT findings (Fig 3). Three parameters differentiated patients with CVID and at least 5 pulmonary nodules quite effectively: (1) CD4⁺:CD8⁺ T-cell ratio higher than 2, (2) history of AIHA or ITP, and (3) serum IgM level higher than 18 mg/dL (Table 3). If none of these parameters were met, a patient was not likely to have nodular lung disease (NPV 80%). Meeting 2 of these parameters increased specificity and PPV to higher than 90%, and the odds for developing nodular lung disease were increased 20-fold. Patients meeting 3 of these parameters had at least 5 pulmonary nodules.

Patients with ground glass opacity were differentiated by a statistically significant elevation in monocytes and decrease in CD19⁺IgM-IgD-CD27⁺ isotype-switched memory B cells (Fig 4). Lower monocyte count was useful for excluding the likelihood of ground glass opacity, because monocytes with no more than 500 cells/ μ L had a NPV of 85% (Table 3). Adding the parameter of lower

than 0.5% CD19⁺IgM-IgD-CD27⁺ isotype-switched memory B cells to this monocyte count increased specificity for ground glass opacity to higher than 90% and the odds of this CT finding 7-fold.

There were no significant differences in serum immunoglobulin (diagnostic IgG, therapeutic IgG, IgA, or IgM) between patients with and those without bronchiectasis, at least 5 pulmonary nodules, ground glass opacity, or no CT findings. However, the highest serum IgM values occurred in patients with at least 5 pulmonary nodules. There were no significant differences in total B cells, IgM⁺CD27⁺ B cells, natural killer cells, eosinophils, or neutrophils.

Lung Pathology

Twelve patients had lung biopsies, all with at least 5 pulmonary nodules on CT scan (Table 4). All patients underwent lung biopsy examination as a result of chest consolidation at CT in the setting of lymphadenopathy to rule out infection and lymphoma and to characterize ILD, if present. Eleven of the 12 biopsies showed PLH,³⁴ and 3 had granulomas. LIP and OP may lead to ground glass opacity on CT scan,^{33,35,36} and this was the case in 4 of 6 patients. Moreover, the finding of LIP and/or OP was statistically associated with a peripheral monocyte count of at least 500 cells/ μ L ($P = .015$).

Discussion

The authors analyzed a group of 61 patients with CVID who had a chest CT scan to seek clinical and/or laboratory correlations with specific radiologic findings. Because CT scan of the chest was not routinely obtained in all patients with CVID, there may have been a bias toward more severe disease in this study because many patients had imaging performed for clinical symptoms.

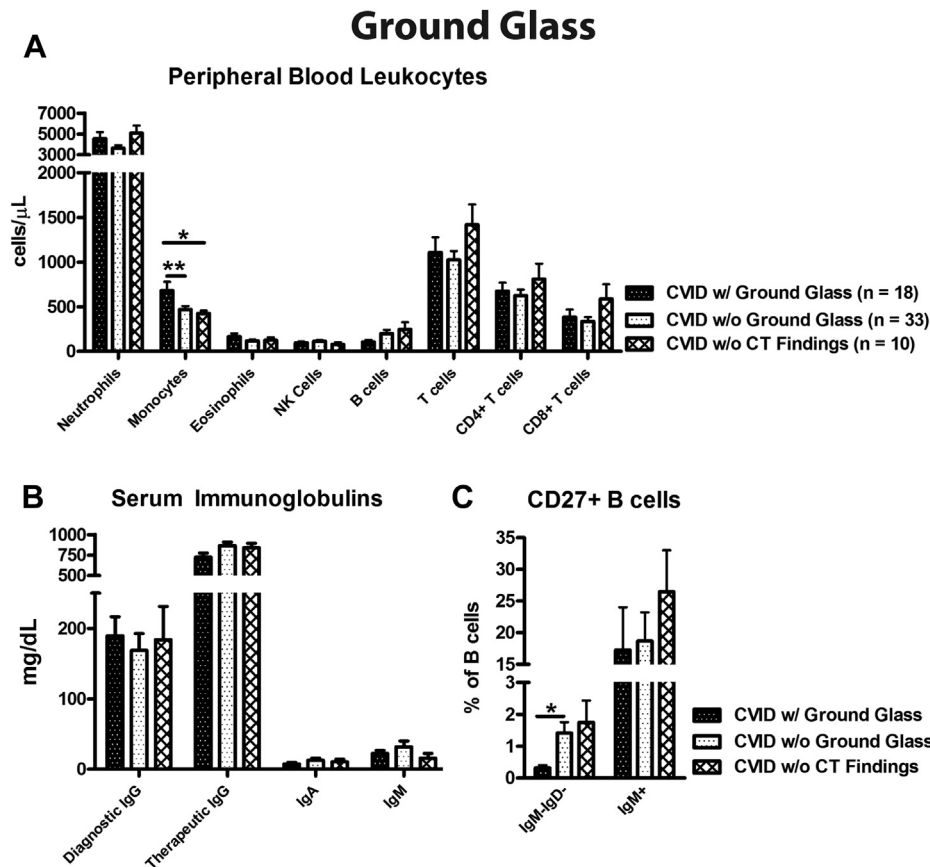


Figure 4. Laboratory associations with ground glass. (A) Peripheral blood leukocytes. (B) Quantitative serum immunoglobulins. (C) CD27⁺ B-cell percentage. * $P < .05$, ** $P < .01$. CT, computed tomography; CVID, common variable immunodeficiency.

Many patients are referred to the authors' institution because of abnormal CT chest scans in the setting of CVID, further contributing to the high prevalence of ILD in this cohort. Indeed, the most frequent radiologic finding in this study, pulmonary nodules, is the most common radiologic presentation of ILD in CVID.^{6,37,38} It is the high prevalence of ILD that allows this study to uniquely classify divergent radiologic manifestations of CVID lung disease.

Those with bronchiectasis only, likely to be the most common radiologic abnormality overall in patients with CVID,³⁷ had the highest prevalence of pneumonia, oldest median age, and lowest percentage of medical complications other than enteropathy. Bronchiectasis has been associated with a history of pneumonia in CVID.³⁸ The high sensitivity of a CD4⁺ T-cell count lower than 700 cells/ μ L in this cohort strongly suggests that lower CD4⁺ T-cell counts heighten susceptibility to bronchiectasis in CVID. Advancing age and history of

Table 4				
Lung pathology				
Patient	Type	Pathology diagnosis	PLH	Granulomas
1	thorascopic	reactive lymphoid hyperplasia	yes	no
2	thorascopic	atypical nodular lymphoid infiltrate with poorly formed granulomas	yes	yes
3	thorascopic	atypical lymphoid hyperplasia	yes	no
4	thorascopic	FB with fibrosis and loosely formed granulomas	yes	yes
5	transbronchial	FB	yes	no
6	thorascopic	atypical reactive lymphoid infiltrate with OP	yes	no
7	thorascopic	LIP with FB	yes	no
8	transbronchial	OP	no	no
9	thorascopic	bronchiocentric interstitial pneumonia with fibrosis, lymphoid hyperplasia, OP, and occasional poorly formed granulomas	yes	yes
10	transbronchial	LIP	yes	no
11	thorascopic	LIP with FB and OP	yes	no
12	transbronchial	atypical lymphoid hyperplasia	yes	no
Parameter	FB or LH only (n = 6)		LIP or OP (n = 6)	P value
≥ 5 Nodules	6		6	1.00
Ground glass	2		4	.567
Monocytes ≥ 500	0		5	.015

Abbreviations: FB, follicular bronchiolitis; LH, lymphoid hyperplasia; LIP, lymphocytic interstitial pneumonia; OP, organizing pneumonia; PLH, pulmonary lymphoid hyperplasia.

pneumonia may compound the susceptibility imparted by a low CD4⁺ T-cell count, as evidenced by the high PPV when these additional parameters are included. Precursor findings to bronchiectasis can be identified on a CT scan of the chest, because bronchial wall thickening with dilation may progress to bronchiectasis.¹⁹ Thus, a low CD4⁺ T-cell count and/or a history of chronic bronchitis or pneumonia in a patient with CVID may suggest the need for interval CT scans of the chest even in the absence of active respiratory symptoms. The European Society for Immunodeficiencies registry recently identified an association between low IgM levels and bronchiectasis in CVID,³⁹ supporting previous reports of a protective role of IgM in the lung.^{23,40} The present study may not have been adequately powered to detect a decreased IgM in patients with bronchiectasis. Further studies are needed to examine the possibility for prevention and treatment of bronchiectasis in CVID, although usage of prophylactic antibiotics⁴¹ and increased immunoglobulin replacement dosage⁴² may be efficacious.

The authors found ILD to be associated with younger age and liver disease, in addition to AIHA and ITP, lymphoid hyperplasia, and splenomegaly or splenectomy as previously reported.^{10,43,44} There was no apparent association of ILD with history of pneumonia or enteropathy. Elevated CD4⁺:CD8⁺ T-cell ratio, serum IgM, and history of AIHA and ITP were strongly associated with extensive pulmonary nodules, which the authors found to almost exclusively represent PLH, as in prior reports.^{6,13} Emergence of PLH can be indicative of more systemic lymphoid hyperplasia, because these patients with CVID also had higher prevalence of hilar adenopathy and splenomegaly or splenectomy. Despite antibody deficiency, PLH in CVID is characterized by actively proliferating ectopic lung follicles,¹³ which may promote expansion of CD4⁺ T cells (vs CD8⁺ T cells) and possibly the IgM elevation noted in this study. Indeed, patients with CVID and lymphoproliferative complications have an increase in activated CD4⁺ T cells,⁴⁵ and higher serum IgM level has been shown to be a predictor of polyclonal lymphocytic infiltration in CVID.³ In addition, the heightened prevalence of AIHA or ITP may be correlated with lymphoid hyperplasia, because benign proliferation in the spleen⁴⁶ or in gastric-associated lymphoid tissue⁴⁷ may be associated with ITP. Clearly, the propensity for many patients with CVID to develop benign lymphoid proliferations deserves further study.⁴⁸

Patients with ground glass opacity could be differentiated by a significantly elevated peripheral blood monocyte count and the largest percentage of concurrent liver disease. Of note, patients in this study with biopsy-proven LIP and/or OP were significantly more likely to have monocytes with at least 500 cells/ μ L, in addition to having ground glass opacity on CT scan. Thus, elevated monocytes may be indicative of an evolution of ILD that manifests as ground glass opacity on CT scan and LIP or OP at biopsy. Of the 61 patients, a lung biopsy had been performed in 12, thus precluding further comments on associations of pathology with the laboratory parameters noted here. It remains to be seen whether similar inflammatory progression underlies granulomatous disease that can occur in the lungs, in addition to the liver, lymph nodes, skin, or spleen of patients with CVID.^{17,49}

The present data suggest parameters that are associated with selected radiologic findings in CVID that may provide insight into the determinants of chronic pulmonary complications in this disease. Although bronchiectasis appears to develop over time as a result of heightened susceptibility to infection, ILD generally occurred in younger patients with CVID and concurrent autoimmunity and lymphoid hyperplasia. Furthermore, a subset of patients with ILD may show progression to a heightened inflammatory state characterized by increased peripheral monocytes, liver involvement, LIP or OP at lung biopsy, and ground glass opacity on CT chest scan. The results of this study suggest that

divergent immunologic processes underlie the distinct clinical manifestations of bronchiectasis and ILD in CVID.

References

- [1] Cunningham-Rundles C, Maglione PJ. Common variable immunodeficiency. *J Allergy Clin Immunol*. 2012;129:1425–1426.e3.
- [2] Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol*. 2009;145:709–727.
- [3] Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood*. 2008;112:277–286.
- [4] Quinti I, Soresina A, Spadaro G, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol*. 2007;27:308–316.
- [5] Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood*. 2012;119:1650–1657.
- [6] Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J Allergy Clin Immunol*. 2004;114:415–421.
- [7] Gregersen S, Aalokken TM, Mynarek G, et al. Development of pulmonary abnormalities in patients with common variable immunodeficiency: associations with clinical and immunologic factors. *Ann Allergy Asthma Immunol*. 2010;104:503–510.
- [8] Arish N, Eldor R, Fellig Y, et al. Lymphocytic interstitial pneumonia associated with common variable immunodeficiency resolved with intravenous immunoglobulins. *Thorax*. 2006;61:1096–1097.
- [9] de Gracia J, Vendrell M, Alvarez A, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol*. 2004;4:745–753.
- [10] Bondioni MP, Soresina A, Lougaris V, Gatta D, Plebani A, Maroldi R. Common variable immunodeficiency: computed tomography evaluation of bronchopulmonary changes including nodular lesions in 40 patients. Correlation with clinical and immunological data. *J Comput Assist Tomogr*. 2010;34:395–401.
- [11] Touw CM, van de Ven AA, de Jong PA, et al. Detection of pulmonary complications in common variable immunodeficiency. *Pediatr Allergy Immunol*. 2010;21:793–805.
- [12] Fernandez Perez ER. Granulomatous lymphocytic interstitial lung disease. *Immunol Allergy Clin North Am*. 2012;32:621–632.
- [13] Maglione PJ, Ko HM, Beasley MB, Strauchen JA, Cunningham-Rundles C. Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2014;133:535–542.
- [14] Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Immunol*. 2010;134:97–103.
- [15] Kohler PF, Cook RD, Brown WR, Manguso RL. Common variable hypogammaglobulinemia with T-cell nodular lymphoid interstitial pneumonitis and B-cell nodular lymphoid hyperplasia: different lymphocyte populations with a similar response to prednisone therapy. *J Allergy Clin Immunol*. 1982;70:299–305.
- [16] Fasano MB, Sullivan KE, Sarpong SB, et al. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. *Medicine (Baltimore)*. 1996;75:251–261.
- [17] Bouvry D, Mouthon L, Brillet PY, et al. Granulomatosis-associated common variable immunodeficiency disorder: a case–control study versus sarcoidosis. *Eur Respir J*. 2013;41:115–122.
- [18] Sugino K, Uekusa T, Homma S. Granulomatous–lymphocytic interstitial lung disease in a patient with common variable immunodeficiency. *Intern Med*. 2013;52:2683–2684.
- [19] Hampson FA, Chandra A, Sreanot NJ, et al. Respiratory disease in common variable immunodeficiency and other primary immunodeficiency disorders. *Clin Radiol*. 2012;67:587–595.
- [20] Wislez M, Sibony M, Naccache JM, et al. Organizing pneumonia related to common variable immunodeficiency. Case report and literature review. *Respiration*. 2000;67:467–470.
- [21] Boujaoude Z, Arya R, Rafferty W, Dammert P. Organising pneumonia in common variable immunodeficiency. *BMJ Case Rep*. 2013;2013.
- [22] Gregersen S, Holm AM, Fevang B, et al. Lung disease, T-cells and inflammation in common variable immunodeficiency disorders. *Scand J Clin Lab Invest*. 2013;73:514–522.
- [23] Carsetti R, Rosado MM, Donnanno S, et al. The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J Allergy Clin Immunol*. 2005;115:412–417.
- [24] Detkova D, de Gracia J, Lopes-da-Silva S, et al. Common variable immunodeficiency: association between memory B cells and lung diseases. *Chest*. 2007;131:1883–1889.
- [25] Sanchez-Ramon S, Radigan L, Yu JE, Bard S, Cunningham-Rundles C. Memory B cells in common variable immunodeficiency: clinical associations and sex differences. *Clin Immunol*. 2008;128:314–321.
- [26] Barbera JA, Hayashi S, Hegele RG, Hogg JC. Detection of Epstein-Barr virus in lymphocytic interstitial pneumonia by in situ hybridization. *Am Rev Respir Dis*. 1992;145:940–946.

- [27] Andiman WA, Eastman R, Martin K, et al. Opportunistic lymphoproliferations associated with Epstein-Barr viral DNA in infants and children with AIDS. *Lancet*. 1985;2:1390–1393.
- [28] Wheat WH, Cool CD, Morimoto Y, et al. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. *J Exp Med*. 2005;202:479–484.
- [29] Prasse A, Kayser G, Warnatz K. Common variable immunodeficiency-associated granulomatous and interstitial lung disease. *Curr Opin Pulm Med*. 2013;19:503–509.
- [30] Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol*. 1999;93:190–197.
- [31] Kainulainen L, Varpula M, Liippo K, Svedstrom E, Nikoskelainen J, Ruuskanen O. Pulmonary abnormalities in patients with primary hypogammaglobulinemia. *J Allergy Clin Immunol*. 1999;104:1031–1036.
- [32] Hare SS, Souza CA, Bain G, et al. The radiological spectrum of pulmonary lymphoproliferative disease. *Br J Radiol*. 2012;85:848–864.
- [33] Lee KS, Kullnig P, Hartman TE, Muller NL. Cryptogenic organizing pneumonia: CT findings in 43 patients. *AJR Am J Roentgenol*. 1994;162:543–546.
- [34] Guinee DG Jr. Update on nonneoplastic pulmonary lymphoproliferative disorders and related entities. *Arch Pathol Lab Med*. 2010;134:691–701.
- [35] Dalvi V, Gonzalez EB, Lovett L. Lymphocytic interstitial pneumonitis (LIP) in Sjogren's syndrome: a case report and a review of the literature. *Clin Rheumatol*. 2007;26:1339–1343.
- [36] Filipek MS, Thompson ME, Wang PL, Gosselin MV, L Primack S. Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus: radiographic and high-resolution CT findings. *J Thorac Imaging*. 2004;19:200–203.
- [37] Obregon RG, Lynch DA, Kaske T, Newell JD Jr, Kirkpatrick CH. Radiologic findings of adult primary immunodeficiency disorders. Contribution of CT. *Chest*. 1994;106:490–495.
- [38] Quinti I, Soresina A, Guerra A, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. *J Clin Immunol*. 2011;31:315–322.
- [39] Gathmann B, Mahlaoui N, Gerard L, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency [published online ahead of print February 27, 2014]. *J Allergy Clin Immunol*. <http://dx.doi.org/10.1016/j.jaci.2013.12.1077>.
- [40] Micol R, Kayal S, Mahlaoui N, et al. Protective effect of IgM against colonization of the respiratory tract by nontypeable *Haemophilus influenzae* in patients with hypogammaglobulinemia. *J Allergy Clin Immunol*. 2012;129:770–777.
- [41] Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA*. 2013;309:1251–1259.
- [42] Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005;94(suppl 1):S1–S63.
- [43] Torigian DA, LaRosa DF, Levinson AI, Litzky LA, Miller WT Jr. Granulomatous-lymphocytic interstitial lung disease associated with common variable immunodeficiency: CT findings. *J Thorac Imaging*. 2008;23:162–169.
- [44] Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood*. 2008;111:77–85.
- [45] Mouillot G, Carmagnat M, Gerard L, et al. B-cell and T-cell phenotypes in CVID patients correlate with the clinical phenotype of the disease. *J Clin Immunol*. 2010;30:746–755.
- [46] Daridon C, Loddenkemper C, Spieckermann S, et al. Splenic proliferative lymphoid nodules distinct from germinal centers are sites of autoantigen stimulation in immune thrombocytopenia. *Blood*. 2012;120:5021–5031.
- [47] Franchini M, Vescovi PP, Garofano M, Veneri D. *Helicobacter pylori*-associated idiopathic thrombocytopenic purpura: a narrative review. *Semin Thromb Hemost*. 2012;38:463–468.
- [48] da Silva SP, Resnick E, Lucas M, et al. Lymphoid proliferations of indeterminate malignant potential arising in adults with common variable immunodeficiency disorders: unusual case studies and immunohistological review in the light of possible causative events. *J Clin Immunol*. 2011;31:784–791.
- [49] Ardeniz O, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. *Clin Immunol*. 2009;133:198–207.