Original Article

Progression of Common Variable Immunodeficiency Interstitial Lung Disease Accompanies Distinct Pulmonary and Laboratory Findings

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What is already known about this topic? Interstitial lung disease frequently complicates common variable immunodeficiency, worsening morbidity and mortality. Immunomodulatory treatment has efficacy in small studies, but adverse effects due to immunosuppression necessitate the identification of patients most appropriate for such therapy.

What does this article add to our knowledge? Interstitial lung disease is progressive in many cases of common variable immunodeficiency. In our cohort, those most likely to have physiologic worsening had a history of severe thrombocytopenia as well as lower immunoglobulin G (IgG) and higher immunoglobulin M (IgM) levels.

How does this study impact current management guidelines? Worsening pulmonary function, increased IgG replacement dosage requirements, severe thrombocytopenia, and elevated serum IgM can be clues to those at greatest risk of physiologic worsening and identify patients for whom immunomodulatory therapy may be indicated.

BACKGROUND: Common variable immunodeficiency may be complicated by interstitial lung disease, which leads to worsened morbidity and mortality in some. Although immunomodulatory treatment has efficacy, choice of patient, duration of treatment, and long-term follow-up are not available. Interstitial lung disease appears stable in certain instances, so it is not known whether all patients will develop progressive disease or require immunomodulatory therapy.

OBJECTIVE: This study aims to determine if all common variable immunodeficiency patients with interstitial lung disease have physiological worsening, and if clinical and/or laboratory parameters may correlate with disease progression.

METHODS: A retrospective review of medical records at Mount Sinai Medical Center in New York was conducted for referred patients with common variable immunodeficiency, CT scan-confirmed interstitial lung disease, and periodic pulmonary function testing covering 20 or more months before immunomodulatory therapy. Fifteen patients were identified from the retrospective review and included in this study.

RESULTS: Of the 15 patients with common variable immunodeficiency, 9 had physiological worsening of interstitial lung disease adapted from consensus guidelines, associated with significant reductions in forced expiratory volume in 1 second, forced vital capacity, and diffusion capacity of the lung for carbon monoxide. Those with progressive lung disease also had significantly lower mean immunoglobulin G levels, greater increases and highest levels of serum immunoglobulin M (IgM), and more significant thrombocytopenia.

CONCLUSION: Interstitial lung disease resulted in physiological worsening in many, but not all subjects, and was associated with suboptimal immunoglobulin G replacement. Those with worsening pulmonary function tests, elevated IgM, and severe thrombocytopenic episodes appear to be at highest risk for progressive disease. Such patients may benefit from immunomodulatory treatment. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:941-50)**

Key words: *Common variable immunodeficiency; CVID; Granulomatous interstitial lung disease; GLILD; Interstitial lung disease; Pulmonary function testing*

Despite being the most common symptomatic primary immunodeficiency, common variable immunodeficiency (CVID) remains an enigma, with surprisingly little understood about its predisposing genetic and immunologic factors.[1,2] CVID is clinically defined by a marked reduction of serum

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Supported by the Jeffrey Modell Foundation, Clinical Immunology Society/Baxter Senior Fellowship Award, Thrasher Research Fund Early Career Award, National Institutes of Health grants AI 048693 and AI 061093, and the David S. Gottesman Immunology Chair.
Conflicts of interest: P. J. Maglione has received research support from the Jeffrey Modell Foundation, Clinical Immunology Society, and Thrasher Research Fund; and has received travel support from the Jeffrey Modell Foundation. J. R. Overbey declares no relevant conflicts. C. Cunningham-Rundles has received research support from the National Institutes of Health; and has received consultancy fees from Kedrion.
Received for publication April 16, 2015; revised manuscript received and accepted for publication July 10, 2015.
Available online September 12, 2015.
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2213-2198
© 2015 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaip.2015.07.004

Abbreviations used
AIHA- Autoimmune hemolytic anemia
CVID- Common variable immunodeficiency
DLCO- Diffusion capacity of the lung for carbon monoxide
FEV1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
Ig- Immunoglobulin
ILD- Interstitial lung disease
ITP- Immune thrombocytopenic purpura
PFTs- Pulmonary function tests

immunoglobulin (Ig) levels coupled with impaired antibody responses to immunization and/or infection.[3] Although the frequency and severity of infections in patients with CVID have significantly improved with the usage of IgG replacement therapy, noninfectious complications of CVID have emerged as the predominant source of morbidity and mortality.[4-7] Noninfectious complications of CVID include autoimmune cytopenias, gastrointestinal inflammatory disease and malabsorption, lung disease, liver disease, and lymphoma, among others.[8,9] The reasons for developing these noninfectious complications, and why only a subset of patients with CVID manifest them, are not known.

Chronic lung disease is among the most common complications of CVID, affecting approximately 30%-60% of patients, depending on the cohort.[6,7,10] Bronchiectasis is likely the most common chronic lung disease in these patients, found in as many of 50% of those with CVID.[11] Interstitial lung disease (ILD) also occurs frequently in CVID and worsens mortality to a greater extent than bronchiectasis.[7,12] Although the true incidence of this complication is not clear because large studies have not distinguished ILD from other forms of chronic lung disease, we found CT evidence of ILD in 39 of 61 patients with CVID examined at our tertiary care center, which suggested that the frequency of this complication may be underestimated.[13] The etiology of ILD in CVID is unclear, and it is notable that bronchiectasis does not progress into ILD in many cases nor is it a prerequisite for ILD development.[11,13,14] However, this does not rule out infection as a cause of ILD, and an association with human herpesvirus 8 has been reported.[15] Alternatively, ILD may be a consequence of generalized benign lymphoproliferation inherent to a subset of patients with CVID,[16] as correlations of ILD with persistent lymphadenopathy and splenomegaly have been reported.[6,12,13,17,18] Along these lines, biopsies of CVID ILD demonstrate benign lymphoproliferative pathology (such as follicular bronchiolitis, lymphocytic interstitial pneumonitis, and nodular lymphoid hyperplasia) in nearly all cases.[12,19,20] Intrinsic immune dysregulation, perhaps in the absence of infection, can result in ILD that is pathologically similar to that seen in CVID. This is demonstrated by the characteristic lymphoproliferative ILD seen in patients with monogenic immune dysregulation disorders such as cytotoxic T lymphocyte-associated protein-4 (CTLA-4) deficiency and signal transducer and activator of transcription 3 (STAT3) gain-of-function mutations as well as autoimmune diseases such as Sjogren's syndrome.[21-24]

Although IgG replacement therapy alone is not believed to be effective in most cases, immunosuppression with cyclophosphamide, cyclosporine, or combination therapy with azathioprine and rituximab has shown efficacy as treatment for CVID ILD.[25-27] However, immunosuppressive therapy carries risks of infection and malignancy, which may be of greater concern in immunocompromised patients.[28,29] As there are reports that CVID ILD is not progressive in some instances, not all cases of CVID ILD may warrant aggressive and potentially risky immunosuppression.[14,30] Moreover, CVID ILD is characterized by heterogeneous pathology, consisting of differing proportions of pulmonary lymphoid hyperplasia, organizing pneumonia, and granulomatous inflammation in individual patients, resulting in the general classification of granulomatous-lymphocytic ILD.[13,30-32] This variable constituency of pathology amongst individual patients may differentially influence the rate of progression and severity of disease. In this study, we culled CVID patients with CT evidence of ILD who had periodic pulmonary function tests (PFTs) over the course of 20 or more months before any immunomodulatory treatment to find clinical and laboratory parameters that might be useful for identifying those at greatest risk for progression of ILD.

METHODS

Study design

This study was conducted via a retrospective review of electronic medical records from Mount Sinai Hospital in New York. Electronic medical records are available for patient encounters or submitted data from January 2003 until present, and are linked with printed records that predate the electronic transition as well as test results and progress notes from referring providers. Patients with the International Classification of Diseases, Ninth Revision Code for CVID (279.06) who had a CT scan of the chest and at least 2 measurements of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) conducted 20 or more months apart found in their medical record were included in this study. In many cases, PFTs were performed by referring physicians, with additional testing conducted at our institution on subsequent occasions. PFTs and other patient data obtained before 6 months of IgG replacement therapy or after immunomodulatory treatment with azathioprine, cyclosporine, cyclophosphamide, mercaptopurine, or rituximab were excluded. 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 $\leq$ 400 mg/dL, IgA $<$ 45 mg/dL, IgM $<$ 35 mg/dL), poor response to vaccines, and exclusion of other causes of hypogammaglobulinemia.[33] Chest CT scans were required to show evidence of ground glass opacity and/or more than 4 nodules of at least 1 mm in diameter for patients to be included. All 15 patients who met these study criteria were included in the final analysis and were lifelong nonsmokers. This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

DATA COLLECTION

Patient age, sex, medication history, PFTs, laboratory values (IgG, IgA, IgM, complete blood count with differential, lymphocyte subsets, alkaline phosphatase), chest CT radiologist report, and pathologist report of lung biopsy were derived from the medical record. Additionally, the history of autoimmune hemolytic anemia (AIHA) or immune thrombocytopenic purpura (ITP), lymphadenopathy and/or splenomegaly, hepatitis or nodular regenerative hyperplasia, enteropathy, and/or malignancy was determined by the review of medical notes and radiology reports.

Statistical analysis

Associations between stable or progressive ILD and categorical clinical parameters were assessed by Fisher exact tests. Differences in continuous laboratory values between the 2 groups were

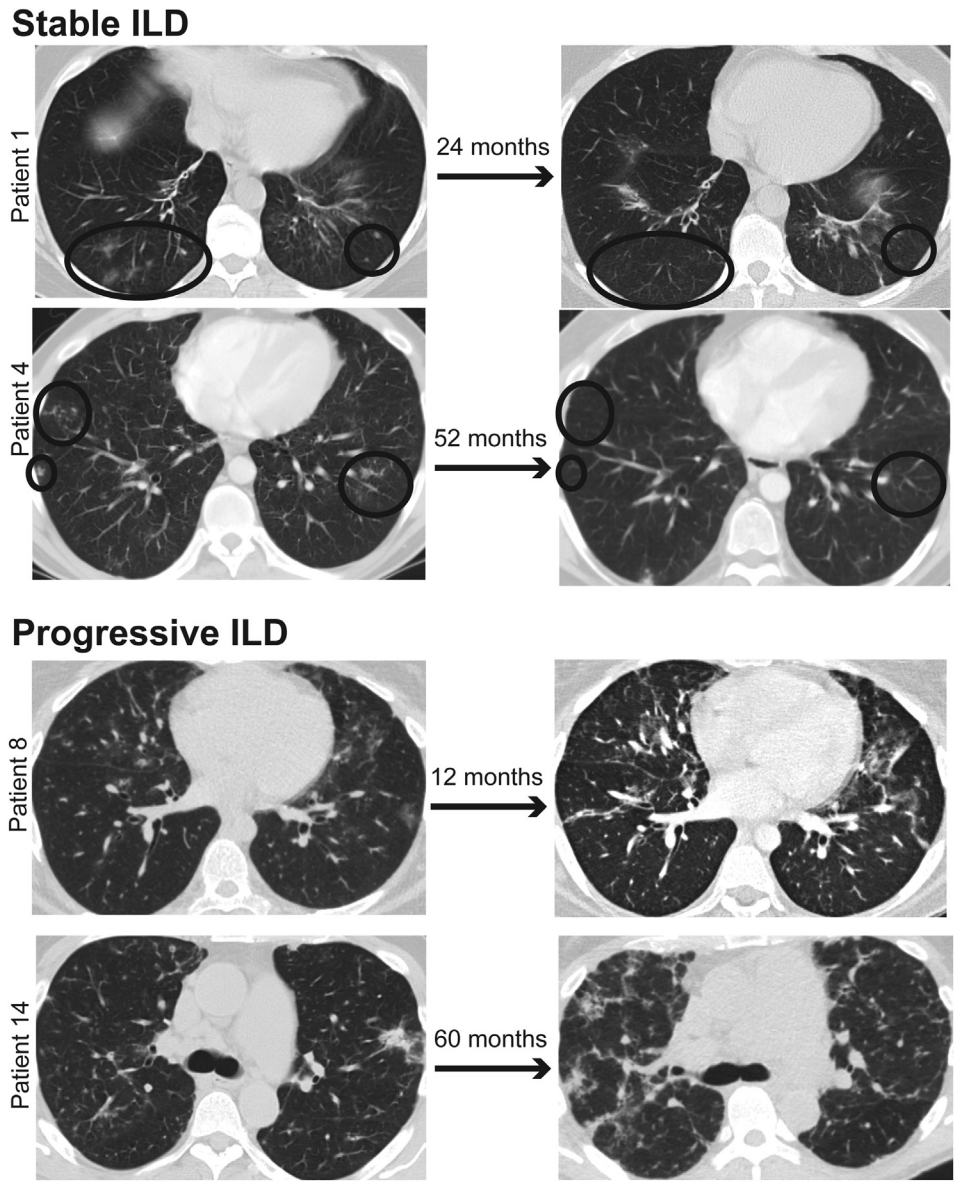

FIGURE 1. CT chest comparison of common variable immunodeficiency (CVID) patients with stable or progressive interstitial lung disease (ILD). CVID patients with stable ILD show waxing-and-waning CT findings over the course of years (demarcated with black circles), whereas those with progressive ILD demonstrate steady and diffuse worsening of interstitial disease.

analyzed using nonparametric Mann-Whitney tests using a significance cutoff of $P = .05$ for each test.

RESULTS

More rapidly progressive ILD occurs in a subset of patients with CVID

To objectively assess whether ILD resulted in physiological worsening in our cohort of patients with CVID, we performed a retrospective study of those with CT-confirmed ILD and PFTs over 20 or more months after at least 6 months of IgG replacement therapy and before intervention with immunomodulatory therapy. Of the 15 patients with CVID meeting the inclusion criteria, 9 were found to have a significant physiological decline over the follow-up period by a definition adapted from consensus guidelines of the absolute decline in FVC percent predicted $\geq$ 10 or the absolute decline in diffusion capacity of the lung for carbon monoxide (DLCO) percent predicted $\geq$ 15 for idiopathic pulmonary fibrosis, also extrapolated to other forms of ILD.[34,35] The decline in FVC percent predicted $\geq$ 10% avoids typical variability of testing because the repeat measurement of FVC differs by less than 10% in 95% of normal subjects. Patients with CVID with physiological worsening by these criteria were denoted as having progressive ILD for the purpose of this study, in contrast to the 6 patients with waxing-and-waning CT findings and more stable PFTs denoted as stable ILD (Figure 1). The individual characteristics of all patients in this study are included in Table I.

TABLE I. Patient characteristics

	Age	Sex	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	CT evidence of ILD	CT evidence of bronchiectasis	Lung biopsy	Pathology diagnosis	Other complications	Medications	Percent change in FVC	Percent change in DLCO	Follow-up (mo)
Stable ILD														
1	43	F	<60	<5	34	Patchy areas of ground glass and solid nodules in right-middle lobe and both lower lobes	Yes	ND	ND	Borderline splenomegaly	Inhaled budesonide/formoterol, prophylactic azithromycin	+3	+33	21
2	44	M	39	44	21	Multiple ill-defined nodules throughout both lungs, lower lobe predominance	No	VATS	FB and nodular LH with rare ill-defined granulomas	ITP, lymphadenopathy	Inhaled fluticasone/salmeterol, prophylactic ciprofloxacin	−7	−5	22
3	45	F	9	<7	15	Patchy centrilobular nodularity throughout both lungs	Yes	EB	FB	Marginal zone B-cell lymphoma (8 y after CVID diagnosis), splenomegaly	Inhaled budesonide, prophylactic azithromycin	+24	ND	144
4	45	M	338	25	35	Numerous subcentimeter ground glass infiltrates in both lower lobe areas	No	VATS	Mixed lymphocytic and granulomatous infiltrate with patchy OP	ITP, lymphadenopathy, splenomegaly	Inhaled budesonide/formoterol, prophylactic azithromycin	0	−2	20
5	65	F	174	39	17	Scattered areas of ground glass opacification seen diffusely within both lungs with superimposed nodular opacities	Yes	VATS	BIP with fibrosis, LH, OP, and occasional poorly formed granulomas	Hepatosplenomegaly, enteropathy	None	−9	−8	79
6	68	F	321	4	4	Extensive bilateral lower lobe infiltrates and scattered bilateral nodularity	Yes	EB	Chronic inflammation with organizing interstitial pneumonitis, no granulomas identified	splenomegaly	Inhaled budesonide/formoterol, prophylactic azithromycin	+12	+31	20
Progressive ILD														
7	26	M	349	0	15	Multiple small nodules with ill-defined borders throughout the lungs bilaterally with areas of ground glass opacification	No	ND	ND	ITP, lymphadenopathy, splenomegaly	None	−26	−51	63
8	31	F	312	16	17	Innumerable nodular densities are noted through both lungs with basilar predominance	Yes	VATS	Atypical nodular lymphoid infiltrate with poorly formed granulomas	ITP, lymphadenopathy, splenomegaly	Inhaled beclomethasone, prophylactic azithromycin	−13	ND	45
9	32	F	217	<7	9	Widespread nodules, areas of airspace consolidation, and ground glass opacities throughout both lungs	Yes	EB	NA, nonmalignant reactive inflammation by report	ITP, lymphadenopathy, splenomegaly, pancytopenia	Inhaled budesonide/formoterol, prophylactic azithromycin	−19	ND	34
10	35	M	400	6	26	Patchy nodular infiltrates in both lungs	No	EB	LIP	ITP, hepatosplenomegaly, lymphadenopathy, NRH	None	−40	ND	80
11	45	M	107	<15	<4	Multiple scattered nodular infiltrates, most are peribronchial but are pleural based in some instances	No	ND	ND	ITP, AIHA, hepatosplenomegaly, lymphadenopathy, LH of parotid gland	Inhaled budesonide/formoterol, prophylactic azithromycin	−22	−16	70
12	48	F	30	6	7	Nodular and irregular consolidative densities throughout the lungs with peripheral predominance	Yes	ND	ND	ITP, splenomegaly, lymphadenopathy	Inhaled budesonide/formoterol, prophylactic azithromycin	−18	−14	50

13	48	M	113	<5	6	Focal consolidations and nodules throughout both lungs	No		EB	Reactive lymphoid tissue and few poorly formed granulomas	Interface hepatitis, hepatosplenomegaly, lymphadenopathy, LH of parotid gland	Inhaled budesonide/formoterol, prophylactic azithromycin	−1	−37	24
14	58	M	57	4	6	Reticulonodular changes seen throughout the lung fields with patchy areas of more dense consolidation	No		ND	ND	ITP, AIHA, hepatosplenomegaly, NRH, prostate cancer	Inhaled budesonide/formoterol, prophylactic azithromycin	−64	−17 (from months 28 to 71)	71
15	61	M	120	2	3	ILD is present that is significantly worse at the lung bases, extensive subpleural interstitial change in both the upper and lower lobes	Yes		ND	ND	ITP, hepatosplenomegaly, lymphadenopathy, NRH	None	−28	−35	48

AIHA Autoimmune hemolytic anemia; *BIP*, bronchiolocentric interstitial pneumonia; *EB*, endobronchial biopsy; *FB*, follicular bronchiolitis; *ITP*, immune thrombocytopenic purpura; *ILD*, interstitial lung disease; *LH*, lymphoid hyperplasia; *LIP*, lymphocytic interstitial pneumonia; *NA*, report not available; *ND*, not done; *NRH*, nodular regenerative hyperplasia; *OP*, organizing pneumonia; *VATS*, video-assisted thoracoscopic surgery.

Interestingly, CVID patients with progressive ILD had significantly higher initial FEV1 ($P = .03$) (Table II). Although not statistically significant, patients with progressive ILD also demonstrated higher initial FVC ($P = .07$), lower initial platelet count ($P = .09$), and more frequent histories of ITP ($P = .09$) and lymphadenopathy ($P = .09$). Moreover, nodular regenerative hyperplasia and chronic noninfectious hepatitis occurred only in those with progressive ILD. Notably, there was no difference among those with stable or progressive ILD for age, sex, presence of bronchiectasis, inhaled corticosteroid or prophylactic antibiotic use (10 patients on azithromycin, 1 patient on ciprofloxacin), initial DLCO, IgG level at diagnosis, or peripheral isotype-switched memory B cells. Likewise, pathologic diagnoses and the presence of granulomas in biopsies did not differentiate those with progressive versus stable ILD.

Changes in pulmonary function over time in patients with CVID ILD

All CVID patients with progressive ILD had a decline in FVC over the course of the study, whereas steady FVC values persisted in those with stable ILD, even markedly improving in 2 cases during the course of the study (Figure 2, *A*). Similarly, FEV1 and DLCO steadily decreased in CVID patients with progressive ILD, but remained unchanged or improved in those with stable ILD. Changes in the FEV1/FVC ratio over time did not notably diverge between those with stable or progressive ILD. Decreases in DLCO preceded significant decreases in FVC in 2 patients (patient 7 and patient 13). Patient 7 had a decrease in DLCO from 113% of predicted to 88%, whereas FVC was virtually unchanged over the first 26 months (99% of predicted to 98%). Patient 12 did not have had worsening of FVC (99% of predicted initially to 98% at the end of the study), but DLCO decreased from 82% to 45% of predicted. There were no instances where FVC significantly decreased without concurrent reduction of DLCO (when measured).

Demonstrating that subjects with CVID can be delineated into 2 ILD subsets based on the PFT criteria of physiological decline, a distinct group with progressive ILD was identified with significantly larger decreases in percent of predicted FVC, FEV1, and DLCO ($P = .002$, $P = .004$, and $P = .005$, respectively) (Figure 2, *B*). There was no significantly different change in FEV1/FVC between CVID patients with stable or progressive ILD. Together these data suggest that there are distinct subsets of patients with CVID ILD with either stable or progressively worsening PFTs defined by the decline in FVC, FEV1, and/or DLCO.

Characteristics of laboratory tests over time in patients with CVID ILD

Serum IgM increases of greater than 20 mg/dL were observed across some time points for 5 of the 9 patients with progressive ILD during the course of the study, but remained unchanged in all of those with stable ILD (Figure 3). Other laboratory values tested did not demonstrate any divergent trends over time between the 2 groups. All patients were on IgG replacement therapy during the course of the study, yet those with progressive ILD had a significantly lower mean serum IgG levels than those with stable ILD ($P = .012$) (Figure 4, *A*). Lower serum IgG levels were found in patients with progressive ILD despite the fact that there was no significant difference in IgG replacement dosage (Figure 4, *B*). The ratio of serum IgG to IgG dosage was significantly lower in those with progressive ILD ($P = .0026$), which demonstrated that these patients require higher dosages of IgG replacement than patients with stable ILD to achieve similar

TABLE II. Comparison of initial clinical and laboratory characteristics

	Progressive (n = 9)	Stable (n = 6)	*P* value
Median age (y)	45	45	.38
Female (%)	3 (33)	4 (67)	.32
CT-confirmed bronchiectasis (%)	4 (44)	4 (67)	.61
History of ITP (%)	8 (89)	2 (33)	.09
History of splenomegaly (%)	9 (100)	5 (83)	.40
History of lymphadenopathy (%)	8 (89)	2 (33)	.09
History of NRH or chronic noninfectious hepatitis (%)	4 (44)	0 (0)	.10
Inhaled corticosteroid usage (%)	6 (67)	5 (83)	.60
Prophylactic antibiotic usage (%)	6 (67)	5 (83)	.60
Initial FEV1 (% of predicted) 25%-75% percentile	84.5-101.5	68.5-88.5	.03
Initial FVC (% of predicted) 25%-75% percentile	85.5-102.5	74.3-86.5	.07
Initial FEV1/FVC (%) 25%-75% percentile	78.0-92.5	75.0-83.8	.12
Initial DLCO (% of predicted) 25%-75% percentile	61.5-89.8	51.0-98.0	1.0
Initial IgG (mg/dL) 25%-75% percentile	82-330.5	31.5-525.3	.96
Initial IgA (mg/dL) 25%-75% percentile	3.0-10.0	4.0-40.3	.19
Initial IgM (mg/dL) 25%-75% percentile	5.0-16.0	12.25-34.3	.10
Initial CD19+ B cells (cells/μL) 25%-75% percentile	3.5-92	25-468	.26
Initial CD27+IgM− B cells (% of CD19+ B cells) 25%-75% percentile	0.44-1.1	0.3-2.0	.95
Initial CD27+IgM+ B cells (% of CD19+ B cells) 25%-75% percentile	11.6-28.3	1.7-34.7	.41
Initial CD4+ T cells (cells/μL) 25%-75% percentile	277-617	436-787	.44
Initial CD8+ T cells (cells/μL) 25%-75% percentile	115-364	141-566	.52
Initial CD4:CD8 ratio 25%-75% percentile	0.95-4.8	1.1-3.3	.79
Initial NK cells (cells/μL) 25%-75% percentile	14-163	24-149	.70
Initial neutrophils (cells/μL) 25%-75% percentile	1595-3950	2890-4100	.20
Initial lymphocytes (cells/μL) 25%-75% percentile	565-1400	700-1860	.74
Initial monocytes (cells/μL) 25%-75% percentile	200-445	319-500	.28
Initial platelets (cells/μL) 25%-75% percentile	74-165	139-229	.09
Initial hemoglobin (G/DL) 25%-75% percentile	12.2-15.2	11-16	.94
Initial alkaline phosphatase (U/L) 25%-75% percentile	74-148	61-170	.59

DLCO, Diffusion capacity of the lung for carbon monoxide; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ITP*, immune thrombocytopenic purpura; *NRH*, nodular regenerative hyperplasia.

serum IgG levels (Figure 4, *C*). Over the course of the study, peak levels of the serum IgM level were significantly higher in patients with progressive ILD compared with those with stable ILD ($P = .02$) (Figure 4, *D*). Changes in leukocyte subsets and platelets (Figure 4, *E*) as well as hemoglobin and serum IgA (data not shown) did not statistically differ between the 2 groups.

As we found lower mean IgG, higher IgM, and lower platelet values to be associated with physiologic worsening of CVID ILD, we looked more closely to determine whether specific values for these parameters were found more commonly in patients with progressive disease. Mean serum IgG levels greater than 700 mg/dL or 1000 mg/dL, typical goals of IgG replacement for patients with conventional and complicated CVID, respectively, were significantly more common in those with stable disease (Table III). Additionally, serum IgM levels greater than the median value of all serum IgM measurements (13 mg/dL) were measured in significantly more patients with progressive ILD, and patients with stable ILD did not have recorded IgM levels above 60 mg/dL, whereas more than half of those with progressive ILD did. Similarly, thrombocytopenic episodes with platelet counts less than the median of all study measurements (112×10^3/μL) were found in patients with significantly more progressive ILD, and platelet counts never dropped below 80×10^3/μL in those with stable ILD during the course of the study.

DISCUSSION

A major goal of this study was to examine whether physiological worsening was observed in all patients in this CVID ILD cohort. Although most patients did have progressive ILD, 6 of 15 subjects did not meet the PFT criteria of physiological worsening over the course of 20 or more months. Although this does not exclude the possibility that patients with stable ILD can worsen at a later time, the fact that 2 subjects did not have significant physiological worsening over more than 6 years of follow-up (up to 12 years in 1 case) suggests that ILD is not necessarily progressive in all patients with CVID. This is consistent with anecdotal reports of others who base treatment decisions on the decline in PFTs rather than radiologic findings alone.[30] Those with stable ILD had waxing-and-waning CT chest findings, a phenomenon that has been observed before in CVID.[17] Yet, our results suggest that ILD is progressive in many, and likely the majority, of patients with CVID. Prior work has reported progressive worsening of PFTs in patients with CVID; however, these studies did not independently evaluate the impact of ILD relative to other chronic lung conditions, such as bronchiectasis.[36,37] We also found that decreases in DLCO preceded drops in FVC in 2 of the patients with progressive ILD, whereas drops in FVC never preceded reductions in DLCO. These data are consistent with prior reports that DLCO is useful in screening and monitoring of CVID lung disease.[14,19,38] In addition to the small study size, our report is limited by referral bias, as our medical center is frequently referred refractory patients with worsening clinical status. Additional studies are necessary to corroborate our findings.

Interestingly, we found that CVID patients with progressive ILD had significantly higher initial FEV1 and FVC values. There are a few potential explanations for this observation. It is possible

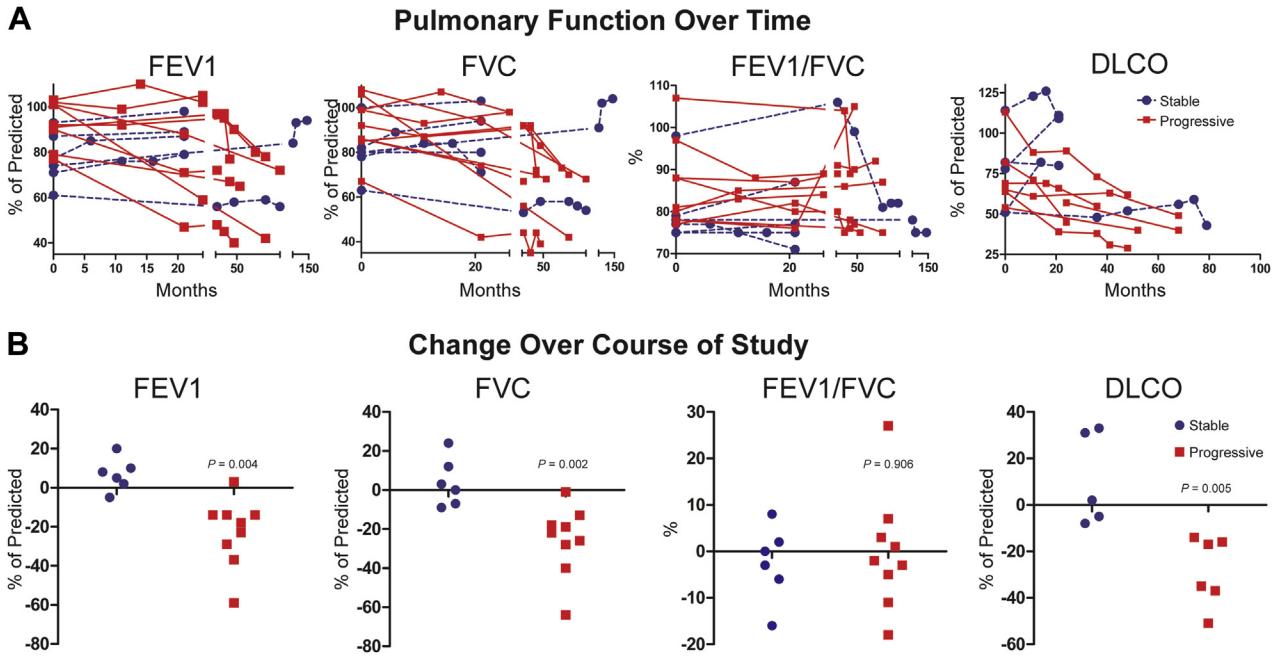

FIGURE 2. **A**, Changes in pulmonary function tests over time. Those with progressive interstitial lung disease (ILD) have precipitous drops in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and diffusion capacity of the lung for carbon monoxide (DLCO) during the course of the study. **B**, Progressive ILD was associated with significantly greater decreases in FEV1, FVC, and DLCO. Common variable immunodeficiency patients with stable ILD are denoted by blue circles, and those with progressive ILD by red squares.

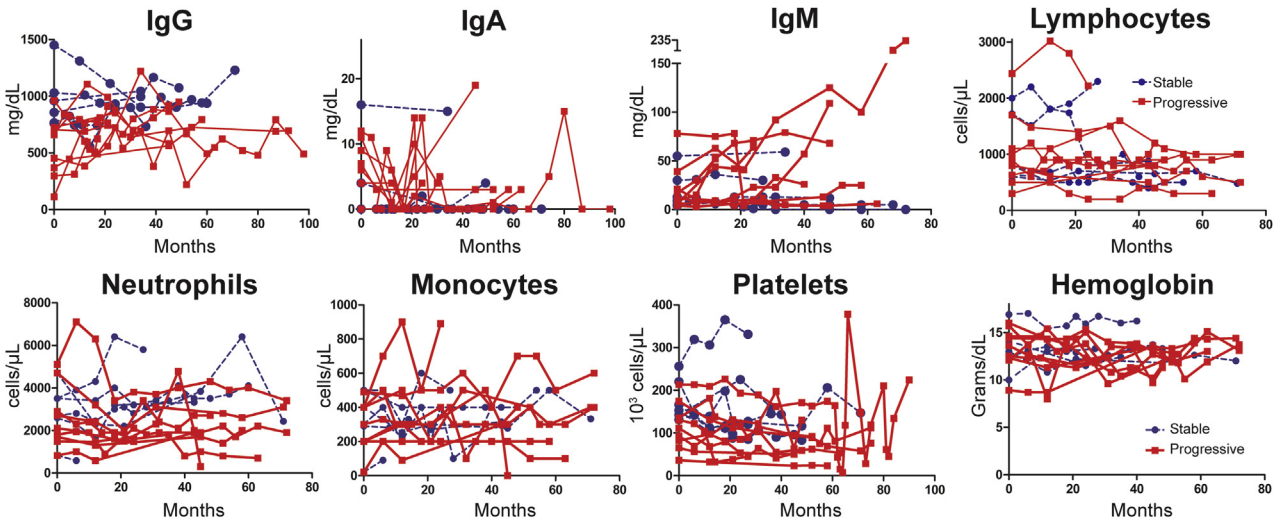

FIGURE 3. Changes in laboratory parameters over time. Serum IgM levels steadily climb in many with progressive interstitial lung disease (ILD), but remain unchanged in those with stable ILD. Common variable immunodeficiency patients with stable ILD are denoted by blue circles, and those with progressive ILD by red squares.

that those with stable ILD had progressive ILD before the initiation of this study. Subsequently, the development of fixed parenchymal changes and fibrosis may limit further worsening of PFTs. However, fibrosis was not apparent on the initial chest CT scans of these patients, and there were no notable differences in the radiologist reports of CT scans between those with chronic or progressive ILD. Additionally, patients with progressive ILD had steadily worsening PFTs through the duration of the study without any apparent plateau of decline; thus, we did not find evidence that ILD progression spontaneously halts in CVID. Alternatively, differences in age may have influenced initial PFT values. Although there was no significant difference in median age between the 2 groups, about half of the subjects with progressive ILD, but none of those with stable ILD, were under the age of 40. Additionally, bronchiectasis could have also contributed to the lower initial PFTs, as bronchiectasis was found in 67% of patients

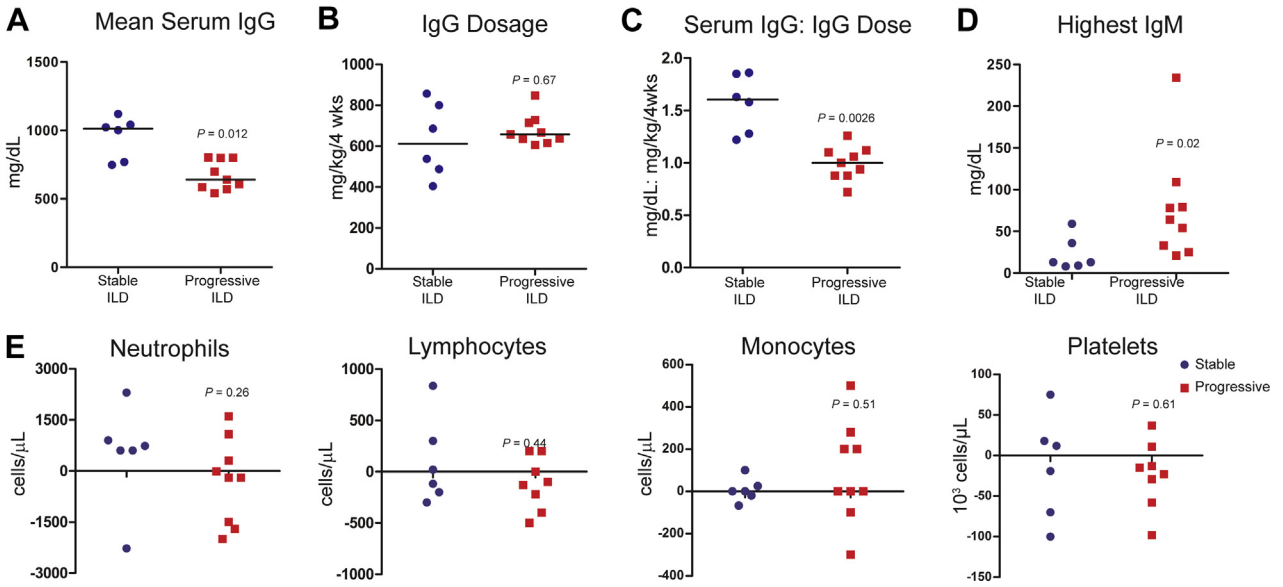

FIGURE 4. **A**, The mean IgG level during the course of the study was significantly lower in those with progressive interstitial lung disease (ILD). **B**, The peak level of serum IgM was significantly higher in patients with progressive ILD. **C-E**, Changes in laboratory parameters over time for other laboratory parameters. Common variable immunodeficiency patients with stable ILD are denoted by blue circles, and those with progressive ILD by red squares.

TABLE III. Specific laboratory values in common variable immunodeficiency interstitial lung disease (ILD)

Lab value	Stable ILD (n = 6)	Progressive ILD (n = 9)	*P* value
Mean IgG (mg/dL)			
IgG > 700	6 (100%)	3 (33%)	0.03
IgG > 1000	4 (67%)	0 (0%)	0.01
Highest IgM (mg/dL)			
>13 (median)	2 (33%)	9 (100%)	0.01
>60	0 (0%)	5 (56%)	0.04
Lowest Plt (10^3/μL)			
<112 (median)	3 (50%)	9 (100%)	0.04
<80	0 (0%)	9 (100%)	0.002

Plt, Platelet.

with stable ILD but only 44% of those with progressive ILD, and may have been more severe in those patients.

Although thrombocytopenia could seem unlikely to be related to ILD, multiple studies have found that these 2 complications are strongly associated in CVID.[18,39] Thrombocytopenia may be due to splenic sequestration as splenomegaly was found in nearly all patients included in this study. Alternatively, autoimmune cytopenias, most commonly manifesting as ITP, may be driven by the same dysregulated lymphoproliferation that leads to ILD.[40] Notably, the concurrence of autoimmune cytopenias and lymphoproliferation is a characteristic of other primary immunodeficiencies with clinical presentations that can be quite similar to CVID, such as autoimmune lymphoproliferative syndrome and CTLA-4 deficiency.[21,22,41] Higher serum IgM appears to be a marker for lymphoproliferative complications in CVID,[6] and we have previously found higher levels of IgM to distinguish CVID patients with ILD from those without ILD.[13] Our small study suggests that serum IgM increases of at least 20 mg/dL in individual patients or IgM levels above the median for subjects in this study (13 mg/dL) may be indicators for those at risk of ILD progression, but larger studies are necessary to confirm these findings. It should be noted that the normal range of serum IgM in healthy adults is approximately 40-300 mg/dL; thus, what is referred to as "high" for patients with CVID may still be below the normal range.

A predominant pathological feature of CVID ILD is ectopic pulmonary B-cell follicles containing germinal centers that act as active centers of cellular proliferation.[19] It may be within these proliferating follicles that B-cell responses are activated, with IgM being the default Ig produced by CVID B cells with limited ability to produce other isotypes. Thus, the elevated serum IgM seen in CVID patients with progressive ILD may be indicative of the inflammatory activation within these ectopic follicles that could drive both ILD and autoimmune cytopenias. Indeed, benign lymphoproliferation has been previously linked with ITP.[40,42] A more extensive study of this residual IgM production in CVID is needed to determine whether it is simply a biomarker of lymphoproliferation and/or inflammation or whether IgM-producing B cells are directly impacting disease.

We found that CVID patients with progressive ILD had lower mean IgG levels than those with chronic ILD. It is impossible to conclude from this retrospective study that such a difference in serum IgG could contribute to ILD progression. However, it is notable that there was no significant difference in IgG replacement dosage between the 2 groups. Rather, our data suggest that those with progressive ILD require higher dosages of IgG replacement, as the ratio of serum IgG to IgG replacement dosage was significantly lower in these patients. CVID patients with GI disease causing extensive IgG loss or those with inflammation markedly increasing catabolism may require higher IgG

replacement dosages. We note here that increasing IgG dosage requirements in a CVID patient with ILD may be indicative that the lung disease is progressive. Although the exact reason why lower IgG replacement dosages were achieved in those with progressive disease is not known, it seems prudent to ensure that customary serum IgG levels are achieved. We suggest that serum IgG levels should be maintained at least 700 mg/dL in patients with CVID ILD, with a goal of 1000 mg/dL strongly considered, as 4 of 6 patients with stable ILD, but no patients with progressive ILD, had mean IgG values greater than 1000 mg/dL. This is similar to the result from a study of 24 adult patients with CVID that found IgG replacement greater than 600 mg/dL to be protective against pulmonary physiological worsening.[37] However, that study did not differentiate the etiology of chronic lung disease, so the benefit of IgG replacement at that dosage may have been due to treatment of bronchiectasis rather than ILD.

It is clear through our experience, and that of others, that although IgG replacement may improve some cases of CVID ILD, the progression of ILD is not altered by this therapy in many instances. Immunosuppressive therapies including corticosteroids, cyclosporine, infliximab, and rituximab have been utilized in such patients, but results with these agents are variable.[25,26,43,44] Combination immunotherapy with azathioprine and rituximab may hold the most promise in treatment of CVID ILD, as this regimen was efficacious in a case series of 7 patients.[27] However, the usage of immunosuppressive therapy in immunocompromised patients may heighten the risk of infection or malignancy.[28,29] As we found that CD4+ T-cell counts below 700 cells/μL raise the risk of bronchiectasis in patients with CVID at our medical center, the usage of immunosuppression to treat CVID lung disease may not be a trivial decision.[13] This current report is a retrospective study of relatively small size from 1 clinical center, so treatment guidelines for CVID ILD cannot be derived from its results. Larger prospective studies are needed to confirm risk factors of disease progression and determine which patients should be treated with immunomodulatory therapy. As there are currently no guidelines for the treatment of CVID ILD, the results of this current study help to inform decisions in CVID ILD management by highlighting that vigilant IgG replacement is a necessity, PFTs are useful for identifying those with progressive ILD and should include DLCO, and severe thrombocytopenia and elevated IgM levels can be clues to those at greatest risk of physiologic worsening.

Acknowledgments

We gratefully acknowledge Lin Radigan for flow cytometry measurement of peripheral B-cell subsets and Laureen Ojalvo for valuable discussion.

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