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Progression of CVID Interstitial Lung Disease Accompanies Distinct Pulmonary and Laboratory Findings

Paul J. Maglione, MD,PhD[a], **Jessica R. Overbey, MS**[b], and **Charlotte Cunningham-Rundles, MD,PhD**[a,c]

[a]Department of Medicine, Division of Clinical Immunology, Icahn School of Medicine at Mount Sinai, New York, NY

[b]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY

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

Abstract

Background—Common variable immunodeficiency may be complicated by interstitial lung disease, leading to worsened morbidity and mortality in some. While 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—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 prior to immunomodulatory therapy. Fifteen patients were identified from the retrospective review and included in this study.

Results—Nine of the 15 common variable immunodeficiency patients had physiological worsening of interstitial lung disease adapted from consensus guidelines, associated with significant reductions in FEV1, FVC, and DLCO. Those with progressive lung disease also had significantly lower mean IgG levels, greater increases and highest levels of serum IgM, and more significant thrombocytopenia.

Corresponding author: Paul J. Maglione, MD, PhD, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1425 Madison Ave, New York, NY 10029. Telephone: 212-659-9243, Fax: 212-987-5593. paul.maglione@mssm.edu.

The authors declare no conflicts of interest.

Conclusion—Interstitial lung disease resulted in physiological worsening in many, but not all subjects, and was associated with suboptimal IgG 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.

Keywords

common variable immunodeficiency; CVID; granulomatous interstitial lung disease; GLILD; interstitial lung disease; pulmonary function testing

INTRODUCTION

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 marked reduction of serum immunoglobulin (Ig) levels coupled with impaired antibody responses to immunization and/or infection.[3] While the frequency and severity of infections in CVID patients have significantly improved with the usage of IgG replacement therapy, non-infectious complications of CVID have emerged as the predominant source of morbidity and mortality.[4–7] Non-infectious 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 non-infectious complications, and why only a subset of CVID patients manifest them, are not known.

Chronic lung disease is among the most common complications of CVID, effecting approximately 30–60% of patients, depending upon 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] While 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 CVID patients examined at our tertiary care center, suggesting 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 CVID patients,[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 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 like Sjogren's Syndrome.[21–24]

While IgG replacement therapy alone is not believed to be effective in most cases, immunosuppression with cyclophosphamide, cyclosporine, or combination therapy with azathioprine and rituximab have 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 interstitial lung disease (GLILD).[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 prior to 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 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 two 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 done by referring physicians, with additional testing conducted at our institution on subsequent occasions. PFTs and other patient data obtained prior to 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 ≤ 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 > 4 nodules of at least 1 mm in diameter for patients to be included. All 15 patients that met these study criteria were included in the final analysis and were lifelong non-smokers. 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, 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 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 two groups were analyzed using nonparametric Mann Whitney tests using a significance cut-off of $P = 0.05$ for each test.

RESULTS

More rapidly progressive ILD occurs in a subset of CVID patients

To objectively assess whether ILD resulted in physiological worsening in our cohort of CVID patients, 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 prior to intervention with immunomodulatory therapy. Of the 15 CVID patients meeting the inclusion criteria, 9 were found to have significant physiological decline over the follow-up period by a definition adapted from consensus guidelines of absolute decline in FVC percent predicted ≥ 10 or absolute decline in DLCO percent predicted ≥ 15 for idiopathic pulmonary fibrosis, also extrapolated to other forms of ILD.[34, 35] Decline in FVC percent predicted ≥ 10% avoids typical variability of testing because repeat measurement of FVC differs by less than 10% in 95% of normal subjects. CVID patients 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.

Interestingly, CVID patients with progressive ILD had significantly higher initial FEV1 ($P = 0.03$) (Table II). Though not statistically significant, progressive ILD patients also demonstrated higher initial FVC ($P = 0.07$), lower initial platelet count (P = 0.09), and more frequent histories of ITP ($P = 0.09$) and lymphadenopathy ($P = 0.09$). Moreover, nodular regenerative hyperplasia and chronic non-infectious hepatitis only occurred 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, initial diffusion capacity of the lung for carbon monoxide (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, while steady FVC values persisted in those with stable ILD, even markedly improving in two cases during the course of the study (Figure 2A). Similarly, FEV1 and DLCO steadily decreased in CVID patients with progressive ILD, but remained unchanged or improved in those with stable ILD. Changes in 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% while 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 end of 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 CVID subjects can be delineated into two ILD subsets based upon 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 ($P = 0.002$, $P = 0.004$, and $P = 0.005$, respectively) (Figure 2B). 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 CVID ILD patients with either stable or progressively worsening PFTs defined by decline in FVC, FEV1, and/or DLCO.

Characteristics of laboratory tests over time in patients with CVID ILD

Serum IgM increases of > 20 mg/dL were observed across some time points for 5 of the 9 progressive ILD patients 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 two 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 ($P = 0.012$) (Figure 4A). Lower serum IgG levels were found in progressive ILD patients despite the fact that there was no significant difference in IgG replacement dosage (Figure 4B). The ratio of serum IgG to IgG dosage was significantly lower in those with progressive ILD ($P = 0.0026$), demonstrating that these patients require higher dosages of IgG replacement than stable ILD patients to achieve similar serum IgG levels (Figure 4C). Over the course of the study, peak levels of serum IgM level were significantly higher in patients with progressive ILD compared to those with stable ILD ($P = 0.02$) (Figure 4D). Changes in leukocyte subsets and platelets (Figure 4E) as well as hemoglobin and serum IgA (data not shown) did not statistically differ between the two 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 conventional and complicated CVID patients 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 while more than half of those with progressive ILD did. Similarly, thrombocytopenic episodes with platelet counts less than the median of all study measurements (112 ×l0^3/μL) were found in significantly more progressive ILD patients and platelet counts never dropped below 80 × 10^3/μL in those with stable ILD during 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. While most patients did have progressive ILD, 6 of 15 subjects did not meet PFT criteria of physiological worsening over the course of 20 or more months. While this does not exclude the possibility that patients with stable ILD can worsen at a later time, the fact that two subjects did not have significant physiological worsening over more than 6 years of follow-up (up to 12 years in one case) suggests that ILD is not necessarily progressive in all CVID patients. This is consistent with anecdotal reports of others who base treatment decisions upon 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 CVID patients. Prior work has reported progressive worsening of PFTs in CVID patients, 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, while 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 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 that those with stable ILD had progressive ILD prior to 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 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. While there was no significant difference in median age between the two groups, about half of the progressive ILD subjects, 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 stable ILD patients but only 44% of those with progressive ILD, and may have been more severe in those patients.

While thrombocytopenia could seem unlikely to be related to ILD, multiple studies have found that these two 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 CVID patients may still be below the normal range.

A predominant pathological feature of CVID ILD are 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] 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 two groups. Rather, our data suggests 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. While the exact reason that lower IgG replacement dosages were achieved in those with progressive disease is not known, it seems prudent to ensure customary serum IgG levels are achieved. We suggest that serum IgG levels should be maintained at least 700 mg/dL in patients with CVTD 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 > 1000 mg/dL. This is similar to the result from a study of 24 adult CVID patients 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 treatment of bronchiectasis rather than ILD.

It is clear through our experience, and that of others, that while 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 raises the risk of bronchiectasis in CVTD patients at our medical center, the usage of immunosuppression to treat CVTD lung disease may not be trivial decision.[13] This current report is a retrospective study of relatively small size from one 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 CVTD 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.

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ABBREVIATIONS

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
GLILD	granulomatous-lymphocytic interstitial lung disease
Ig	immunoglobulin
ILD	interstitial lung disease
ITP	immune thrombocytopenic purpura
PFTs	pulmonary function tests

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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 history of severe thrombocytopenia as well lower IgG and higher 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 which immunomodulatory therapy may be indicated.

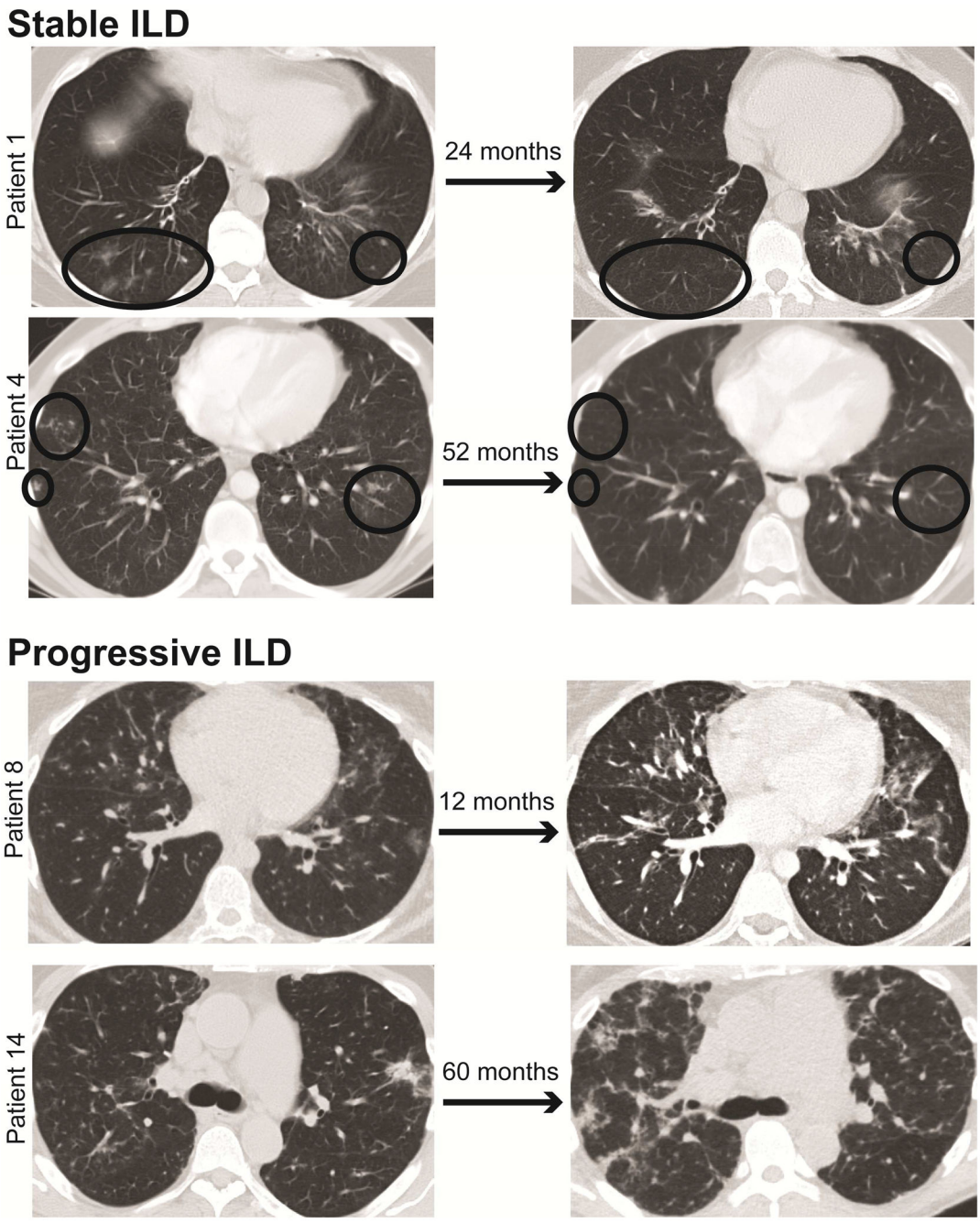

Figure 1.

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

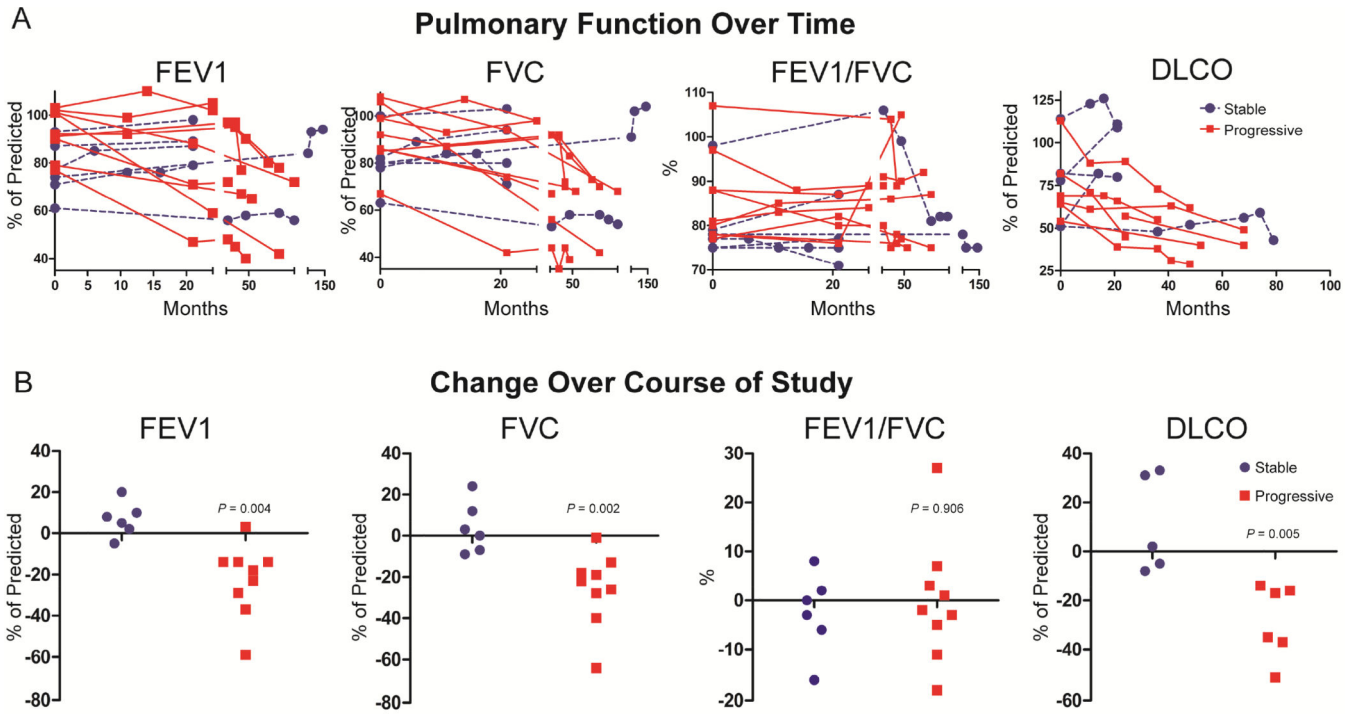

Figure 2.

A. Changes in PFTs over time. Those with progressive ILD have precipitous drops in FEV1, FVC, and DLCO during the course of the study. B. Progressive ILD was associated with significantly greater decreases in FEV1, FVC, and DLCO. CVID patients with stable ILD are denoted by blue circles, progressive ILD are red squares.

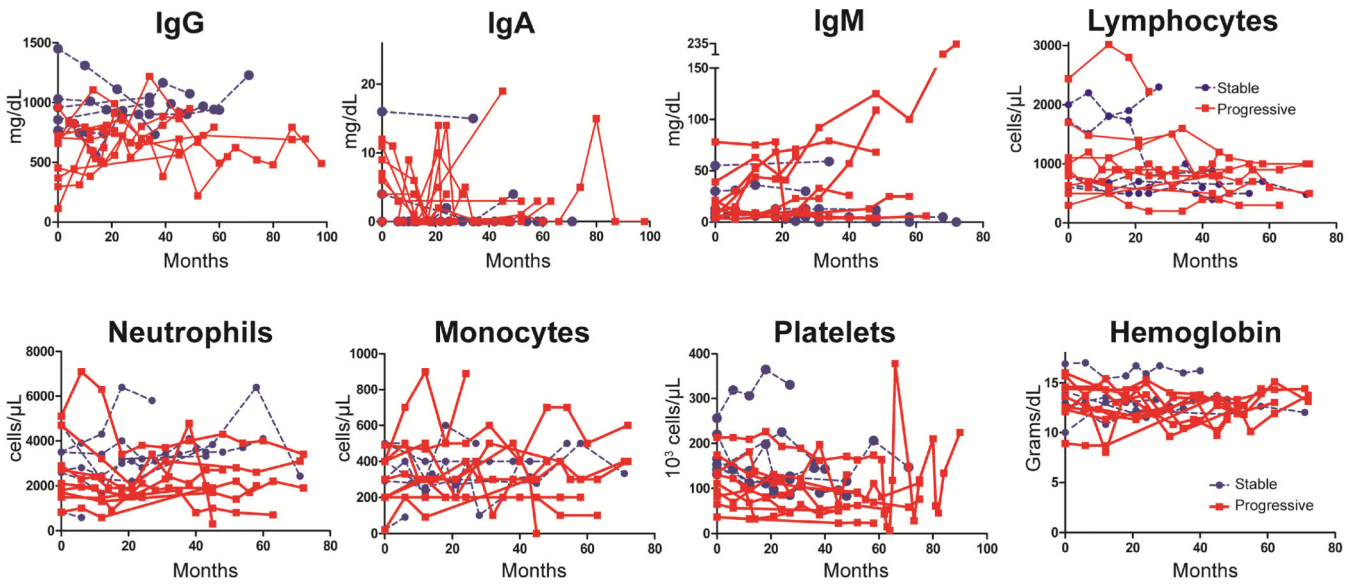

Figure 3.

Changes in laboratory parameters over time. Serum IgM levels steadily climb in many with progressive ILD, but remain unchanged in those with stable ILD. CVID patients with stable ILD are denoted by blue circles, progressive ILD are red squares.

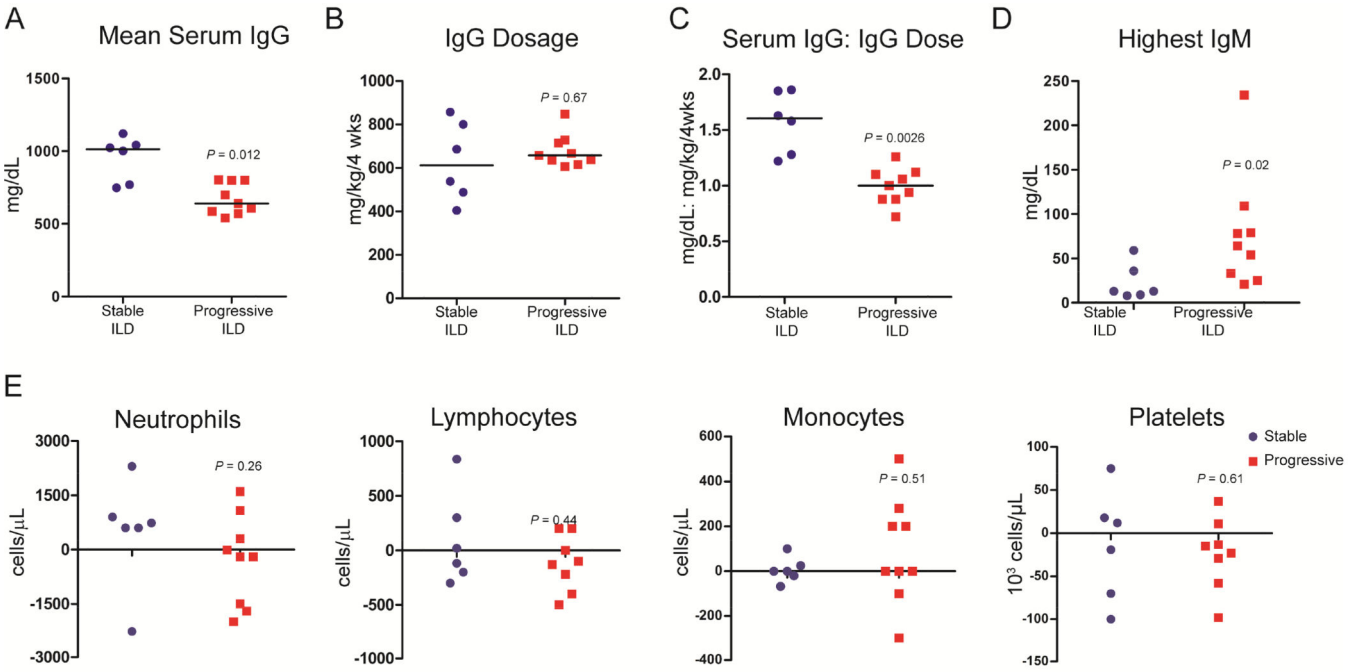

Figure 4.

A. The mean IgG level during the course of the study was significantly lower in those with progressive ILD. B. The peak level of serum IgM was significantly higher in patients with progressive ILD. C. Changes in laboratory parameters over time for other laboratory parameters. CVID patients with stable ILD are denoted by blue circles, progressive ILD are red squares.

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	% Change in FVC	% Change in DLCO	Follow-up (months)
Stable ILD														
1	43	F	<60	<5	34	Patchy areas of groundglass 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 years 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	hepato-splenomegaly, enteropathy	none	−9	−8	79

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	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	% Change in FVC	% Change in DLCO	Follow-up (months)
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-	no	ND	ND	ITP, lymphadenopathy,	none	−26	−51	63
						defined borders throughout the lungs bilaterally with areas of ground glass opacification				splenomegaly				
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 groundglass opacities throughout both lungs	yes	EB	NA, non-malignant 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, hepato-splenomegaly, lymphadenopathy, NRH	none	−40	ND	80
11	45	M	107	<15	<4	Multiple scattered nodular infiltrates, most are peribronchial but are	no	ND	ND	ITP, AIHA, hepato-splenomegaly, lymphadenopathy, LH of parotid gland	Inhaled budesonide/formoterol, prophylactic azithromycin	−22	−16	70

	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	% Change in FVC	% Change in DLCO	Follow-up (months)
						pleural based in some instances	pleural based in some							
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, hepato-splenomegaly, 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, hepato-splenomegaly, 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, hepato-splenomegaly, lymphadenopathy, NRH	none	−28	−35	48

AIHA, autoimmune hemolytic anemia; BIP, brochiolocentric 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

Table II

Comparison of Initial Clinical and Laboratory Characteristics

	Progressive (n = 9)	Stable (n = 6)	*P*value
Median Age (years)	45	45	0.38
Female (%)	3 (33)	4 (67)	0.32
CT-confirmed Bronchiectasis (%)	4 (44)	4 (67)	0.61
History of ITP (%)	8 (89)	2 (33)	0.09
History of Splenomegaly (%)	9 (100)	5 (83)	0.40
History of Lymphadenopathy (%)	8 (89)	2 (33)	0.09
History of NRH or Chronic Non-Infectious Hepatitis (%)	4 (44)	0 (0)	0.10
Inhaled Corticosteroid Usage (%)	6 (67)	5 (83)	0.60
Prophylactic Antibiotic Usage (%)	6 (67)	5 (83)	0.60
Initial FEV1 (% of predicted) 25% – 75% Percentile	84.5 – 101.5	68.5 – 88.5	0.03
Initial FVC (% of predicted) 25% – 75% Percentile	85.5 – 102.5	74.3 – 86.5	0.07
Initial FEV1/FVC (%) 25% – 75% Percentile	78.0 – 92.5	75.0 – 83.8	0.12
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	0.96
Initial IgA (mg/dL) 25% – 75% Percentile	3.0 – 10.0	4.0 – 40.3	0.19
Initial IgM (mg/dL) 25% – 75% Percentile	5.0 – 16.0	12.25 – 34.3	0.10
Initial CD19+ B cells (cells/μL) 25% – 75% Percentile	3.5 – 92	25 – 468	0.26
Initial CD27+IgM- B cells (% of CD19+ B cells) 25% – 75% Percentile	0.44 – 1.1	0.3 – 2.0	0.95
Initial CD27+IgM+ B cells (% of CD19+ B cells) 25% - 75% Percentile	11.6 – 28.3	1.7 – 34.7	0.41
Initial CD4+ T cells	277 – 617	436 – 787	0.44

	Progressive (n = 9)	Stable (n = 6)	*P*value
(cells/μL) 25% - 75% Percentile			
Initial CD8+ T cells (cells/μL) 25% – 75% Percentile	115 – 364	141 – 566	0.52
Initial CD4:CD8 Ratio 25% – 75% Percentile	0.95 – 4.8	1.1 – 3.3	0.79
Initial NK Cells (cells/μL) 25% – 75% Percentile	14 – 163	24 – 149	0.70
Initial Neutrophils (cells/μL) 25% – 75% Percentile	1595 – 3950	2890 – 4100	0.20
Initial Lymphocytes (cells/μL) 25% – 75% Percentile	565 – 1400	700 – 1860	0.74
Initial Monocytes (cells/μL) 25% – 75% Percentile	200 – 445	319 – 500	0.28
Initial Platelets (cells/μL) 25% – 75% Percentile	74 – 165	139 – 229	0.09
Initial Hemoglobin (G/DL) 25% – 75% Percentile	12.2 – 15.2	11 – 16	0.94
Initial Alkaline Phosphatase (U/L) 25% – 75% Percentile	74 – 148	61 – 170	0.59

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

Table III

Specific Laboratory Values in CVID 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