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Common Variable Immunodeficiency Associated With Noninfectious Pulmonary Complications and Its Treatment: Beyond Immunoglobulin Therapy

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ABSTRACT

Common variable immunodeficiency (CVID) is a type of primary immunodeficiency that presents as a heterogenous disorder characterized by hypogammaglobinemia, poor response to vaccines, recurrent sinopulmonary infections, and can have noninfectious systemic manifestations. We performed a single-center, retrospective, observational study of five patients with noninfectious complications of CVID. All patients had CVID as defined by the European Society of Immunodeficiencies criteria and had received intravenous immunoglobulin therapy. There were multiple pulmonary manifestations of CVID including frequent pneumonias, bronchiectasis, granulomatous lung disease, and pulmonary hypertension. All our patients were treated with pulmonary vasodilators for severe precapillary pulmonary hypertension along with individualized immunosuppression regimen for interstitial lung disease. Despite treatment for interstitial lung disease and PH, their conditions worsened over 2–3 years with all patients progressing toward organ transplant evaluation. Idiopathic thrombocytopenia and non-cirrhotic portal hypertension were common, with three patients probably suffering from nodular regenerative hyperplasia. Noninfectious complications of CVID can affect different organs and progress despite advanced therapies. Single or multiorgan transplantation is a treatment option for patients with end-stage organ involvement refractory to medical therapy.

1 | Introduction

Primary immunodeficiencies were first recognized in 1952 as a collection of diseases often from monoallelic mutations in inflammatory genes resulting in decreased ability to fight infection, sometimes associated with autoimmunity [1]. Common variable immunodeficiency (CVID) accounts for roughly 15.4% of total primary immunodeficiencies, and up to 50% of symptomatic primary immunodeficiencies [1–3]. The lack of familiarity with the disease leads to significant delays in diagnosis with both the European Society of Immunodeficiencies and a recent report showing between a 4.2 and 7.46-year delay in diagnosis [4, 5]. In a cohort of 457 patients diagnosed with CVID, 57.8% were diagnosed in adulthood [6, 7]. Diagnosing CVID is challenging, requiring a high clinical suspicion. Each year in delay of diagnosis leads to a 1.4% increase in mortality [5]. Approximately 70%

Abbreviations: CTLA-4, cytotoxic T lymphocyte associated protein 4; CVID, common variable immunodeficiency; GL-ILD, granulomatous lymphocytic interstitial lung disease; ILD, interstitial lung disease; PH, pulmonary hypertension; WHO, World Health Organization.

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of patients with CVID develop noninfectious complications, frequently respiratory and autoimmune disease. The presence of these complications is associated with reduced quality of life and worse prognosis [8, 9]. In a study of 902 patients with CVID, 249 (29%) had autoimmune disease, 205 (23%) had bronchiectasis, and 81 (9%) had granulomatous disease [5]. The rates of bronchiectasis in CVID vary with some studies indicating it is seen in up to 50% of patients [10].

Infectious complications of CVID are prevented by immunoglobulin replacement, pooled immunoglobulin G (with trace amounts of immunoglobulin A and M in most products) from donors. Immunoglobulin replacement doses for immunodeficiencies are generally lower than those for autoimmune disease and this lifelong therapy is repeated at predetermined intervals that vary between weekly and monthly depending on the chosen product [11]. Immunoglobulins can be administered intravenously or subcutaneously [5].

CVID is associated with several pulmonary diseases. Over half of patients with CVID are noted to have abnormal pulmonary function testing with both obstructive and restrictive patterns seen [12]. Obstructive lung patterns are seen in bronchiectasis and are often found in older patients with CVID [13]. Restrictive lung patterns are seen in granulomatous lymphocytic interstitial lung disease (GL-ILD). GL-ILD is a distinct clinic-radio-pathological disease that is a diagnosis of exclusion characterized by the presence of both granulomatous and lymphoproliferative manifestations, seen in anywhere from 8% to 22% of patients with CVID [14, 15].

Current guidelines for the management of GL-ILD are based on expert opinion due to the lack of robust scientific evidence [14, 16, 17]. The British consensus protocol for GL-ILD recommends initiating treatment with corticosteroids in patients who are symptomatic or have abnormal or deteriorating lung function. In patients who failed to induce or maintain remission with steroids, the addition of second-line agents such as azathioprine, rituximab, and mycophenolate is recommended [14, 16–19]. Other less common second-line agents that can be considered include abatacept, sirolimus, and cyclosporine [16, 17, 19].

Pulmonary hypertension (PH) is sometimes seen in CVID. The lowest estimated prevalence of PH in CVID patients is 0.37%, which is several times higher than idiopathic pulmonary arterial hypertension (IPAH) in the general population [20, 21]. Treatment of PH in CVID is left to expert opinion due to the lack of robust scientific evidence. Treatment with pulmonary vasodilators has been described in a few case reports, mostly in those who have concomitant GL-ILD. The use of intravenous epoprostenol led to the normalization of brain natriuretic peptide and improvement in right ventricle systolic function in 1 patient with CVID-PH and GL-ILD [22]. Inhaled iloprost has also demonstrated improvement in hemodynamics on right heart catheterization in another patient with CVID-PH [23].

We describe the first case series of noninfectious complications in CVID in the United States. This study underscores the complexity of these cases, focusing on evaluating and managing their pulmonary manifestations. It also highlights the necessity for a multidisciplinary treatment approach, given the potential progression toward solid organ transplantation.

2 | Materials and Methods

This is a retrospective observational study of patients followed at our institution's allergy/immunology, PH, interstitial lung disease (ILD), and lung transplant clinics. A description of clinical and laboratory findings was performed by review of their electronic medical records. Patients were known by the specialists and thus no database was used to identify patients. The Henry Ford Health Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice (#16942). Consent for publication was obtained from our patients.

3 | Results

3.1 | Patient Characteristics

From 2010 to 2024, we identified five patients with chronic hypoxemic respiratory failure secondary to lung manifestations from CVID. All patients met the diagnosis of probable CVID from the European Society of Immunodeficiencies criteria [24]. Our patients' demographic data are listed in Table 1 along with pertinent information regarding their diagnosis of CVID.

Three patients had moderate to severe restrictive disease on pulmonary function tests. Patient 3 had a mixed obstructive-restrictive defect, likely due to prolonged tobacco use and smoking-related ILD, as confirmed by his explanted lung pathology. Patient 5 showed an isolated reduction in DLco with normal spirometry values. Computed tomography (CT) of the chest consistently revealed diffuse bilateral interstitial thickening, both central and subpleural, along with ground glass opacities, nodules, and traction bronchiectasis. All patients required oxygen supplementation for the treatment of chronic hypoxic respiratory failure.

All five patients have ILD and although some of our patient's clinical statuses prevented complete phenotyping, GL-ILD was the confirmed or the most likely diagnosis in all cases by utilization of the consensus definition of GL-ILD proposed by the British Lung Foundation/United Kingdom Primary Immunodeficiency Network [14]. Patient 1 did not have a thorough evaluation of her ILD before transplant; however, on review of pre-transplant CT chest imaging, there were findings of lower lobe predominant traction bronchiectasis, subpleural reticulation, and scattered lung nodules supporting a diagnosis of GL-ILD. Patient 2 was determined to meet the clinical and radiographic criteria for diagnosis of GL-ILD by a multidisciplinary ILD team. Patient 3 had ILD with findings of bilateral centrilobular ground glass nodularities in the upper lobes, mid and upper lung reticulation, and lower lobe bronchial thickening, which likely represents GL-ILD (Figure 1). Patient 4 had a surgical lung biopsy done, which showed nodular lymphoid hyperplasia with immunohistochemistry negative for pulmonary extramarginal zone lymphoma of mucosa-associated lymphoid tissue. These findings plus a radiographic pattern showing diffuse adenopathy and reticulonodular interstitial disease are consistent with GL-ILD. Patient 5 has similar radiographic findings of diffuse bilateral ground glass opacities, bibasilar traction bronchiectasis, and enlarged mediastinal lymph nodes. Due to the severity of the lung disease, a lung biopsy was not routinely obtained in these patients.

TABLE 1 | Baseline clinical characteristics.

Sex	Patient 1 F	Patient 2 F	Patient 3 M	Patient 4 F	Patient 5 F
Age at diagnosis of CVID	24	34	50	49	42
IgG level at diagnosis (mg/dL) Normal range 700–1600 mg/dL		205	405		
Age at diagnosis of ILD	36	40	47	45	38
Age at diagnosis of PH	42	39	47	58	44
Lung function at time of PH diagnosis					
FVC mL (%pred)		1160 (35)	3030 (68)	1830 (54)	2710 (82)
FEV1 mL (%pred)		1010 (37)	1480 (43)	1490 (57)	2050 (75)
FEV1/FVC		87	49	82	83
DLco %pred		25	32	41	45
FVC/DLco		1.5	2.1	1.1	1.8
Evidence of Idiopathic thrombocytopenia (ITP)	No	Yes	Yes	Yes	Yes
Non-cirrhotic portal hypertension	Yes	Yes	No	No	Yes
Suspected nodular regenerative hyperplasia (NRH)	Yes	Yes	No	No	Yes

Abbreviations: DLco, diffusion capacity; FEV1, forced volume in 1-second; FVC, forced vital capacity.

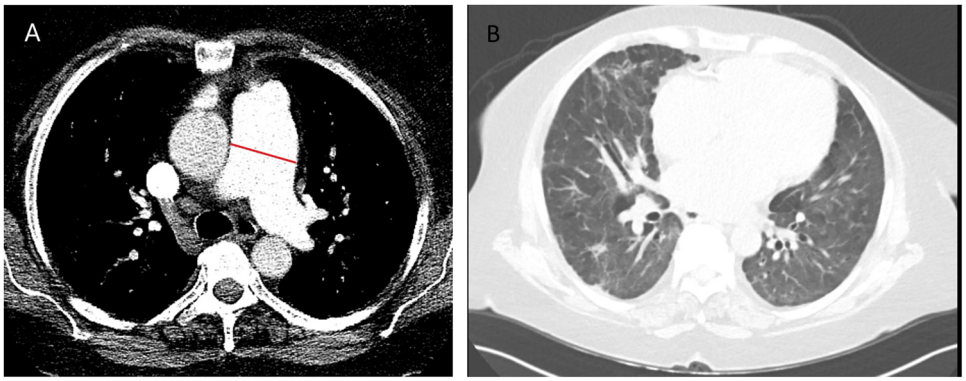

FIGURE 1 | (A) Computed tomography scan showing dilation of the pulmonary artery. (B) Radiographic changes consistent with GL-ILD with bronchiectasis, peribronchovascular reticular opacities seen alongside ground glass opacification and mosaic attenuation.

All five patients had severe precapillary PH on diagnosis, as defined by the 2022 European Society of Cardiology/European Respiratory Society guidelines [21]. Hemodynamics from right heart catheterization at the time of diagnosis showed on average a pulmonary artery systolic pressure of 88 (range 69–114 mmHg), mean pulmonary artery pressure of 56 (range 42–79 mmHg), pulmonary capillary wedge pressure of 12 (range 2–20 mmHg), cardiac index < 2.0 L/min, and pulmonary vascular resistance of 11.3 (range 7.6–14 Wood units). On transthoracic echocardiography, all had severe dilation of the right ventricle with systolic dysfunction and evidence of increased pulmonary afterload.

Our patients developed several important non-pulmonary complications of CVID including three patients with non-cirrhotic portal hypertension, which was attributed to nodular regenerative hyperplasia. These patients had radiographic evidence of portal hypertension with no evidence of cirrhosis on ultrasound. Patients 1 and 2 underwent dual organ transplants with bilateral lung and liver transplants with their explant histopathology showing mild perisinusoidal inflammation of the liver and changes of pulmonary arteriopathy in their lung explants (Figure 2).

3.2 | Patients' Management and Outcomes

All patients required supplemental oxygen during their treatment for chronic hypoxic respiratory failure and received immunoglobulin replacement. For ILD, all patients were initially treated with systemic corticosteroids. This was followed by or used in combination with various other immunosuppressants including mycophenolic acid, rituximab, azathioprine, and abatacept depending on the treatment response, as induction and maintenance or based on a specific genetic abnormality. Patient 4 underwent genetic testing and was found to have a haploinsufficiency of cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Abatacept, a protein with the fragmented crystallizable region of the immunoglobulin G1 fused to CTLA-4, was used in this patient as previous studies showed that abatacept was associated with improvement in both lung function and

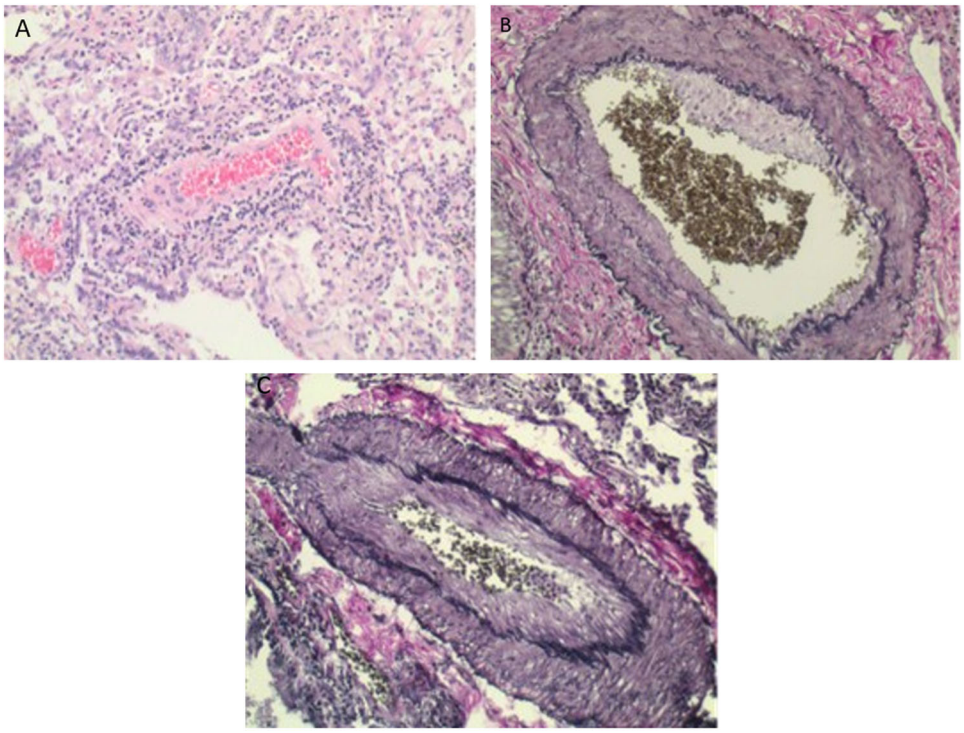

FIGURE 2 | (A) Explanted lung pathology from Patient 3. Perivascular lymphocytic infiltrates seen around pulmonary arteriole. (B) and (C) Two separate foci of pulmonary arterioles with elastic stain showing medial hypertrophy and intimal thickening.

radiographic findings by preventing excessive T lymphocyte proliferation [25, 26]. Our patients' PH was managed with a combination of oxygen therapy, loop diuretics, and pulmonary vasodilators. Due to their severe PH, prostacyclins were commonly used in combination with PDE-5 inhibitor and endothelin receptor antagonists or ERA. Inhaled Treprostinil was used in three patients and IV Treprostinil in one patient (Table 2). Patients receiving pulmonary vasodilators had initial reduction in their serum brain natriuretic peptide levels, improvement in right heart function on transthoracic echocardiography, improved distances on 6-min walk test, and initial improvements in diffusing capacity of the lung for carbon dioxide on pulmonary function testing. Two patients underwent follow-up cardiac catheterization at regular intervals, which showed improved hemodynamics (Figure 3). Despite several lines of therapy, their refractory hypoxic respiratory failure and associated persistent severe PH with right ventricular dysfunction warranted referral for organ transplant evaluation in all five patients.

The presence of non-cirrhotic portal hypertension presumed from nodular regenerative hyperplasia was the reason for dual organ (liver-lung) transplantation in Patients 1 and 2. Patient 5 is also under consideration for a liver–lung transplant. Patient 3 underwent a bilateral lung transplant 5 months ago and Patient 4 is under evaluation for a bilateral lung transplant.

4 | Discussion

Noninfectious complications with multiorgan involvement are described in these five patients with CVID. GL-ILD, PH, idiopathic thrombocytopenia (ITP), and non-cirrhotic liver disease were present in our patients. Based on expert guidance, their GL-ILD was treated with systemic steroids, and all required either the addition or substitution of steroid-sparing immunosuppressants. Patient 4 illustrates how genetic workups in patients with CVID can potentially guide therapy, such as using abatacept in CVID patients with CTLA-4 haploinsufficiency.

All our patients had severe pre-capillary PH, which is congruent with the largest study looking at PH in CVID patients. In this cohort of PH-CVID, Thore et al. from the French PH network found that monotherapy or combination pulmonary vasodilators using a PDE-5 inhibitor and endothelin receptor antagonist was the main treatment for nine out of 10 patients [27]. A difference between our patient cohort and the one from the French registry is the association with GL-ILD, which was present in all five patients in our cohort. PH was described as a late complication. The confirmation of PH and ILD in our patients often occurred around the same time, and sometimes shortly after the diagnosis of CVID, which might be attributed to the nature of our reference center and the delayed diagnosis of CVID. Interestingly one patient was diagnosed with CVID after his diagnosis of PH despite a clinical history of frequent respiratory infections. This highlights the poor recognition of this disease process that is a major contributor to the disease severity seen at diagnosis of advanced lung disease.

Although the severity of PH at diagnosis in our patients often justifies the use of parenteral prostacyclin, concerns about worsening oxygenation due to V/q mismatch (particularly in patients with hypoxia and significant lung parenchyma abnormalities) and infection complications associated with intravenous administration made this treatment approach less favored. Nonetheless, Patient 5 remains stable on IV Treprostinil, similar to the case described by Huston et al. [22] and the

TABLE 2 | Management of CVID and noninfectious complications.

Treatment IVIG	Patient 1 Yes	Patient 2 Yes	Patient 3 Yes	Patient 4 Yes	Patient 5. Yes
Corticosteroids (induction and maintenance)	No	Induction; intermittent use	Yes, tapering	Induction; intermittent use	Yes, intermittent use
Mycophenolic acid (maintenance)	No	Yes (re-started after treatment discontinuation and ILD progression)	No	No	No
Rituximab (maintenance)	No	Yes	No	Yes	Yes
Azathioprine (maintenance)	No	No	No	Yes (stopped due to pancytopenia)	No
Abatacept	No	No	No	Yes	No
Oxygen therapy (max flow L/min)	5 LPM	8 LPM then 15 LPM immediately before lung transplant	15 LPM	3 LPM	6 LPM
RHC					
RAP (mmHg)	9	2	5	12	17
PAP (mmHg)	98/43 (61)	69/26 (42)	81/41 (54)	81/28 (47)	114/59 (79)
PCWP (mmHg)	13	2	10	15	20
CO (L/min)	4.31	2.8	3.2	4.1	2.27
PA Sat%	—	63	64	59	
PVR (WU)	10.2	14	13.4	7.6	11.2
Treprostinil (max dose)	No	Inhaled (360 μg or 15 breaths q6hs)	Inhaled (256 μg or 64 μg per breath q6hs)	Inhaled (144 μg or 6 breaths q6hs, discontinued)	Intravenous (80 ng/kg/min)
Endothelin receptor antagonist	No	Ambrisentan 10 mg daily	Ambrisentan 10 mg daily	No	Macitentan 10 mg daily
PDE-5 inhibitor	No	Sildenafil 20 mg tid	Sildenafil 20 mg tid	No	Tadalafil 40 mg daily
Age at initiation of transplant work up	44	40	50	50	50
Transplant status	Dual organ transplant (liver and bilateral lung) in 2013; died over 9 years post-transplant	Dual organ transplant (liver and bilateral lung)	Recipient of bilateral lung transplant	Evaluated for lung transplant; not currently listed	Evaluated for lung transplant; not currently listed

Note: TTE, values obtained by echocardiography. Oxygen flow in liters per minute (LPM); q6hs and tid, administration frequency four times and three times daily, respectively.
Abbreviations: CO, cardiac output; PAP, pulmonary arterial pressure, in parentheses, mean PAP; PA Sat%, pulmonary artery oxygen saturation; PCPW, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance in Wood unit (WU); RAP, right atrial pressure; RHC, right heart catheterization.

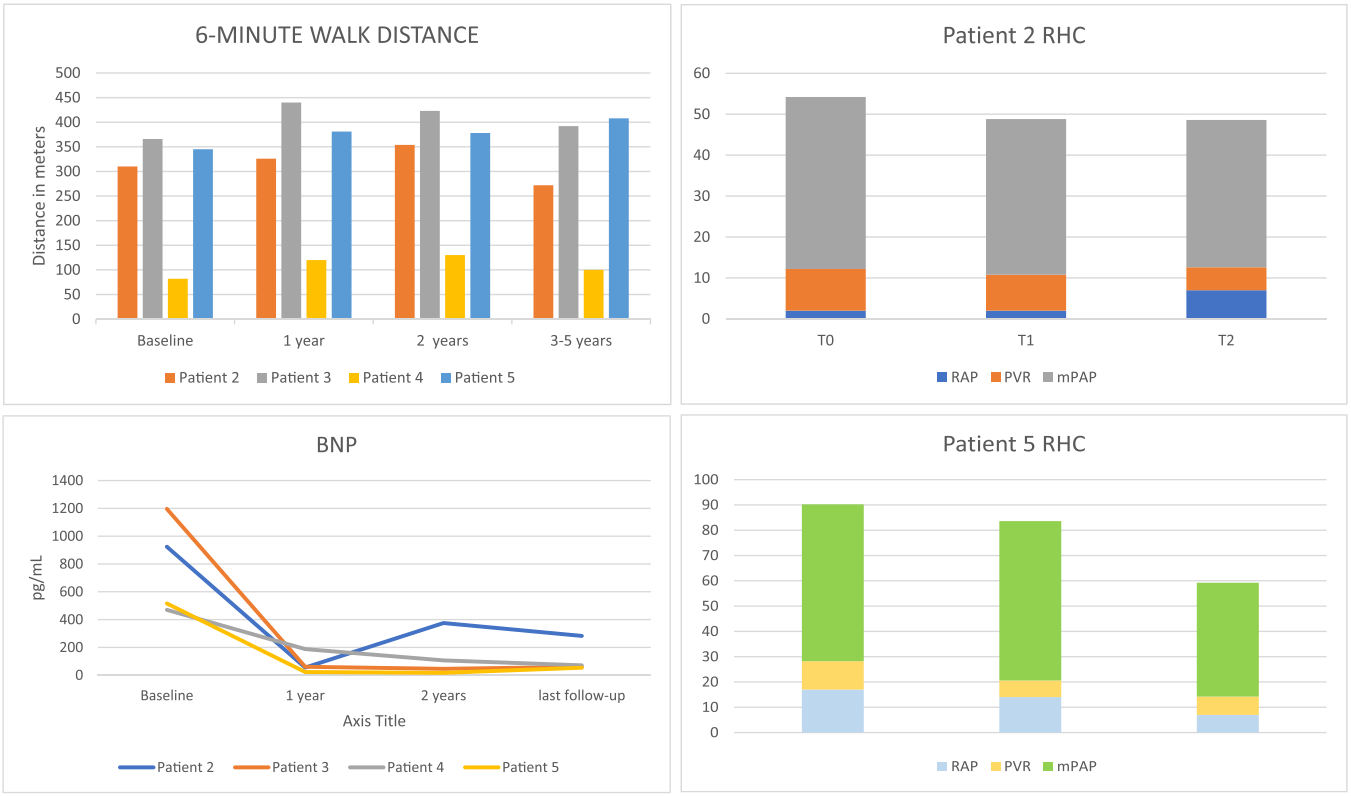

FIGURE 3 | Treatment response based on walking distance; BNP, brain natriuretic peptide and changes in hemodynamics by RHC at baseline, 2 and 3 years on combined pulmonary vasodilators. T0, baseline; T1, 2 years; and T2, 3 years after initiation of pulmonary vasodilators.

other three tolerated well a combination of inhaled prostacyclin, PDE-5 inhibitor, and ERA without worsening hypoxia.

Despite good tolerance with associated initial clinical and hemodynamic improvement with pulmonary vasodilator therapy, their PH remained severe. Although there is no expert guidance for the route of immunoglobulin replacement in patients with CVID and comorbid PH, subcutaneous immunoglobulin may be better tolerated in these patients who have right ventricle dilation and severe PH given a lower fluid amount with this route of administration. Before PH was diagnosed in Patient 5, the administration of intravenous immunoglobulin (IVIG) led to cardiogenic shock with fluid overload 2 years after initiation of therapy for CVID.

Patient 2 had progressing right ventricular enlargement and increasing estimated pulmonary arterial pressure on echocardiography associated with worsening radiographic changes after being off mycophenolic acid. However, when our patients' PH course worsened, it did not always correlate with worsening parenchymal lung disease, suggesting in some cases an independent process. Three of our patients did not show worsening of their parenchymal lung disease while their PH symptoms and echocardiography progressed or remained severe. Before being diagnosed with PH, Patient 3 experienced worsening dyspnea and hypoxia despite a stable pulmonary function test and unchanged parenchyma abnormalities in his CT chest imaging. Echocardiography was followed by right heart catheterization, which confirmed a new diagnosis of PH. He eventually underwent a bilateral lung transplant, about 4 years after his PH diagnosis. His explanted pathology is seen in Figure 2. His lung tissue showed both medial and intimal hyperplasia of the bilateral pulmonary arteries with perivascular lymphocyte infiltrates. These findings of pulmonary arteriopathy are similar to those described by Huston et al. in two patients with PH from CVID [22].

In these patients with CVID, chronic hypoxia, portal hypertension, and inflammation associated with ILD probably contribute significantly to the development of PH. Given the complex mechanisms underlying its development, CVID-associated PH is categorized as belonging to Group V of the World Health Organization (WHO) [21]. Although CVID-PH is not always associated with GL-ILD, such as seen in the results from the French PH Network results, all our patients had ILD. The presence of pulmonary vasculopathy with arteriolar remodeling was the reason to treat their severe PH with pulmonary vasodilators. Due to the common presence of lung parenchyma and airway disease, inhaled Treprostinil was chosen as the first-line treatment in three patients who received treatment for PH. The choice of inhaled Treprostinil was guided by the INCREASE trial, which showed a significant improvement in clinical parameters and a decrease in clinical worsening compared to placebo in patients with PH and ILD [28]. A subgroup analysis of the INCREASE trial described a significant improvement in lung function, which calls to question if inhaled treprostinil has the potential for an anti-inflammatory and anti-fibrotic effect to specifically benefit a subgroup of patients with idiopathic pulmonary fibrosis [29].

Besides the subset of hypoxic CVID patients who develop PH secondary to their parenchymal lung disease as seen in

severe GL-ILD, there is perhaps another subset where inflammation plays a key role in the pulmonary remodeling process that causes severe arteriopathy [22]. It would stand to reason that like in sarcoidosis, another granulomatous inflammatory disease, the pathophysiology at play in CVID PH is multifactorial. A potential common pathophysiologic link between the inflammation in CVID-PH is found in regulatory T cells, a specific type of CD4+ cell. CVID patients with autoimmune symptoms have been shown to have lower circulating CD4+ levels and specifically lower CD4 + CD25+FoxP3+ T-regulatory cell levels than CVID patients without autoimmunity [30–32]. Decreased regulatory T-cell frequency and function has been shown to cause PH in animal models and is seen in disease states that are frequently associated with Group 1 PH such as scleroderma, polymyositis, and across multiple connective tissue disease-associated PH [33–36]. If the underlying inflammatory mechanisms of pulmonary vascular remodeling in PH are shared among different conditions, newly developed drugs like sotatercept and seralutinib could also be options to treat CVID-PH [37].

Careful evaluation of possible multiorgan involvement in CVID is of utmost importance as some patients could progress toward the need of organ transplant. Lung transplantation in CVID has been done successfully for refractory respiratory failure secondary to CVID [38]. Like previous studies, we note a clear association between CVID and autoimmune cytopenia as at least four of our five patients with GL-ILD also had ITP [39]. Liver disease, including NRH, is estimated to affect one-third of patients with CVID [40]. NRH does not have explicit associations with PH but has been noted in patients with PH previously and is usually diagnosed after the diagnosis of PH [41]. The recognition of CVID as a condition that can affect different organ systems and by different mechanisms is particularly important as some patients may progress toward end-stage lung and liver disease [42].

The major concern for most transplant centers is post-transplant infections with added immunosuppression with antirejection therapy in these patients with underlying immunodeficiency.

Our first dual organ transplant patient died from complications of septic shock 9.5 years after organ transplantation.

Despite maximal treatment of patients' CVID, PH, and GL-ILD, all patients have clinical deterioration and progression. By the time of this writing, three patients have undergone bilateral lung transplantation, with two of them requiring dual organ transplant with bilateral lung and liver transplant.

5 | Conclusion

CVID should be considered in patients who have frequent infections or granulomatous disease. Physicians providing care for patients with CVID should be aware of the noninfectious complications in CVID such as PH, GL-ILD, portal hypertension, and ITP.

We additionally noted worsening PH in those with stable parenchymal lung disease and unchanged hypoxemia, suggesting that PH in CVID is not solely attributable to the progression of ILD with worsening hypoxia. The pathophysiology that drives severe PH in patients who have CVID is unclear but likely multifactorial. If the underlying inflammatory mechanisms play a role in pulmonary vascular remodeling in CVID-PH, new treatments that restore T-regulatory cell dysfunction could help treat PH. More research is needed to answer this question, but restoration of the T-regulatory cell balance could be an area of future PH research.

We are limited in that this is an observation study with a few patients.

Author Contributions

Dr. Parsons and Dr. Franco conceived the study design, collected data, and drafted the manuscript; Dr. Parsons and Dr. Franco performed statistical analysis and interpreted results; Dr. Parsons, Dr. Franco, Dr. Hameed, and Dr. Abu Sayf revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

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Disclosure

Dr. Austin Parsons accepts full responsibility for the accuracy and integrity of the data presented in this study and is the guarantor of this manuscript.

Ethics Statement

This study was approved by the IRB with approval number (#16942) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants before data collection.

Conflicts of Interest

The authors declare no conflicts of interest.

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