Granulomatous Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency: A Single Center Experience

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ABSTRACT **Background:** Common variable immunodeficiency (CVID) is the most common clinically significant primary immunodeficiency disorder, typically presenting with hypogammaglobulinemia and recurrent infections. Mechanistically, CVID is caused by abnormal B-cell maturation or function. These abnormalities lead to an impaired ability to generate a normal quantity or diversity of antibodies and an impaired response to neo-antigens. In addition to the resulted immunodeficiency, CVID can also involve immune dysregulation affecting different organ systems, with the lungs being one of the more commonly involved organs. Granulomatous lymphocytic interstitial lung disease (GLILD) is a challenging and well known CVID-related complication. It is associated with high morbidity and increased risk of mortality.

Objectives: To describe the clinical and immunological features of five CVID patients with radiologic and/or pathologic features consistent with granulomatous lymphocytic interstitial lung disease.

Methods: We conducted a review of clinical, laboratory, imaging, and pathology data, as well as B-cell and T-cell immunophenotyping of patient PBMCs, focusing on unique characteristics of CVID GLILD patients.

Results: CVID GLILD patients showed several clinical characteristics, including multiorgan involvement with cytopenias and lymphoproliferation but without significant gastrointestinal involvement. B-cell phenotyping showed abnormal B-cell maturation and development with severely impaired class switching. In addition, unique T-cell phenotype with low to near-absent naive $CD4^+$ T cells was observed.

Conclusions: Lung involvement in the form of GLILD is associated with significant co-morbidity and typical B-cell and T-cell immunophenotyping. Patients should be actively screened for the possibility of GLILD, especially when regularly performed lymphocyte immunophenotyping suggests similar patterns.

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KEY WORDS: common variable immunodeficiency (CVID), granulomatous lymphocytic interstitial lung disease (GLILD), immune dysregulation, inborn errors of immunity (IEI)

Common variable immunodeficiency (CVID) is one of the more common inborn errors of immunity (IEI) disorders. It is characterized by recurrent infections, mostly recurrent sinopulmonary infections and immune dysregulation in the form of either autoimmunity or lymphoproliferation. In many cases, it is a combination of the three [1,2]. The estimated incidence of CVID ranges between 1:10,000 and 1:100,000 [3]. The age of onset is variable with most patients being diagnosed during the third and fourth decade of life [3,4]. Despite being a common immunodeficiency disorder, the diagnosis of CVID is often delayed by a median of 3–7 years due to low level of awareness or suspicion. This delay may result in a prolonged diagnostic odyssey and often incorrect treatments, leading to potential complications and end-organ damage.

CVID diagnosis is based on a combination of clinical and laboratory criteria, which according to the European Society for Immunodeficiencies (ESID) include the following: relevant clinical presentation in the form of recurrent infections and/or autoimmune/inflammatory manifestations, decreased antibody levels, impaired humoral response in the form of either abnormal response to vaccines or abnormal B-cell immunophenotyping with low percent of class-switched memory B cells, and exclusion of alternative explanation and of profound T-cell deficiency [5]. As for the underlying etiology, despite extensive studies, causative genetic defects can be identified in only 25–30% of cases [6], the majority of which are in genes responsible for normal B-cell development [6,7], with variant in *TNFRSF13B* (encoding TACI), *NFKB1*, and *NFKB2* being the most commonly identified [6,8].

In addition to infectious complications due to antibody deficiency, CVID is characterized by a high incidence of immune dysregulation, which could affect different organ systems. It is estimated that more than half of the patients present with at least one form of non-infec-

tious inflammatory/autoimmune manifestations, which in some of the cases could be the central or presenting symptom [6,9]. A recent literature review, summarizing data of 92 selected citations, showed lymphoproliferation or splenomegaly in a median of approximately 35% of patients, gastrointestinal involvement in a median of approximately 30%, liver involvement with hepatomegaly or portal hypertension in 21%, cytopenias in 18%, and lung involvement in the form of asthma in a median of 30.5%, and bronchiectasis in 27% [10].

Granulomatous lymphocytic interstitial lung disease (GLILD) or interstitial lung disease (ILD) were reported in a lower median prevalence of 8.7%. However, GLILD was associated with a significantly high risk of mortality (hazard ratio [HR] 4.9; 95% confidence interval [95% confidence interval [95%CI] 1.6–14.4), second only to lymphoma (HR 5.5, 95%CI, 2.4–12.7) [10].

According to a joint consensus statement of the British Lung Foundation and the United Kingdom Primary Immunodeficiency Network, GLILD is defined as "a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded" [11]. Therefore, to establish a definitive GLILD diagnosis, both radiologic and pathologic evaluation is required.

In the current study, we described our cohort of GLILD patients, focusing on their clinical presentation, co-morbidities, and immune phenotyping.

PATIENTS AND METHODS

PATIENTS

Clinical, laboratory, imaging, and pathology data of five patients with definitive or highly likely GLILD, who were diagnosed between the years 2021 and 2026, were reviewed. GLILD was considered highly likely or definitive based on the joint consensus statement of the British Lung Foundation and the United Kingdom Primary Immunodeficiency Network, which required supporting radiologic and pathologic findings. Four of the five patients (patients 1-4) were defined as definitive GLILD (based on radiologic and pathologic evidence), while patient 5 was defined as highly likely GLILD based on radiologic findings in the absence of tissue sample evaluation. Patients were identified within our clinic CVID patient population. The study was approved by our local institutional review board.

IMMUNOPHENOTYPING

Peripheral blood mononuclear cells (PBMCs) were isolated from fresh blood samples using Ficoll density gradient centrifugation and were stored in liquid nitrogen for later use. B-cell and T-cell immunophenotyping was performed as part of the regular clinical immune evaluation of patients with suspected CVID, which was unrelated to the diagnosis of GLILD. For this purpose, PBMCs were thawed and stained. Cells were acquired using a BD FACSCanto II flow cytometer and data analysis performed using FlowJo softwareV10.0, TreeStar (BD Biosciences, USA).

RESULTS

PATIENT DESCRIPTION AND CLINICAL PRESENTATION

Patient 1

A 41-year-old male first presented at the age of 39 years with cervical lymphadenopathy. Further imaging demonstrated cervical, mediastinal and retroperitoneal lymphadenopathy, mild splenomegaly (15 cm) [Figure 1H], with chest computed tomography (CT) showing multiple pulmonary nodules and bronchiectasis [Figure 1A, 1F]. Immune workup revealed significant hypogammaglobulinemia with IgG of 293 mg/dl (and evidence for low total protein approximately 10 years prior). Biopsies reveal multiple non-caseating granulomas with a dominant population of CD19/CD20 B cells and no evidence for clonality. Immunoglobulin replacement therapy (IgRT) was initiated, without additional immunosuppressive treatment due to normal pulmonary function tests (PFTs) and a normal diffusion capacity of 95% [Table 1].

Patient 2

A 60-year-old female first presented at the age of 30 years with immune thrombocytopenic purpura (ITP), which responded well to a limited course of systemic steroids. Around the age of 50 years the patient developed more severe thrombocytopenia (4 K/μL), had a partial response to steroids and one course of rituximab, but improved with thrombomimetics, which she has continued. In addition, she presented with recurrent pneumonia at least twice a year, responding well to a combination of antibiotics and systemic steroids. Chest imaging 3 years ago showed multiple lung nodules and interstitial lung disease [Figure 1B] with biopsy showing chronic inflammation consisting of small lympho-

Table 1. Patient description and main clinical symptoms

Patient	Sex	Age*	Initial presenting symptom	Infections	Antibody levels**	Age at GLILD, in years	Main pulmonary findings	Lymphoproliferation	Autoimmune cytopenia	Gastrointestinal involvement	Endocrinopathy	Other
1	Male	39	Cervical LAD	Recurrent sinusitis	IgG 293 IgM 6.4 IgA 9.4	39	Multiple bilateral lung modules and bronchiectasis	Lymphadenopathy and splenomegaly	–	–	–	–
2	Female	30	ITP	Recurrent pneumonia	IgG 316 IgM 27 IgA 9	60	Multiple bilateral lung modules and interstitial changes	Lymphadenopathy and splenomegaly	ITP	–	Hypothyroidism	Post removal of conjunctival SCC
3	Female	52	Chronic cough and dyspnea	Recurrent pneumonia	IgG 375 IgM 73 IgA undetected	56	Multiple bilateral lung modules and bronchiectasis	Lymphadenopathy and hepto-splenomegaly	ITP	Occasional diarrhea, mild increase in duodenal IELs	–	Mild neutropenia and lympohopenia (absolute CD4 count of 140/µL
4	Female	25	Recurrent pneumonia	Recurrent pneumonia	IgG ~200	46	Multiple bilateral lung modules, infiltrates, and bronchiectasis	Lymphadenopathy and splenomegaly	–	–	Hypothyroidism	–
5	Male	12	ITP	Chronic cough	IgG 319 IgM 30 IgA 26/4	X	Multiple bilateral lung modules and interstitial changes	Lymphadenopathy and splenomegaly	AHA + ITP	–	–	Kabuki Syndrome

*Age at presentation, in years

**Antibody levels (mg/dl) at presentation

AIHA = autoimmune hemolytic anemia, GLILD = granulomatous lymphocytic interstitial lung disease, ITP = immune thrombocytopenic purpura, LAD = lymphadenopathy, SCC = squamous cell carcinoma

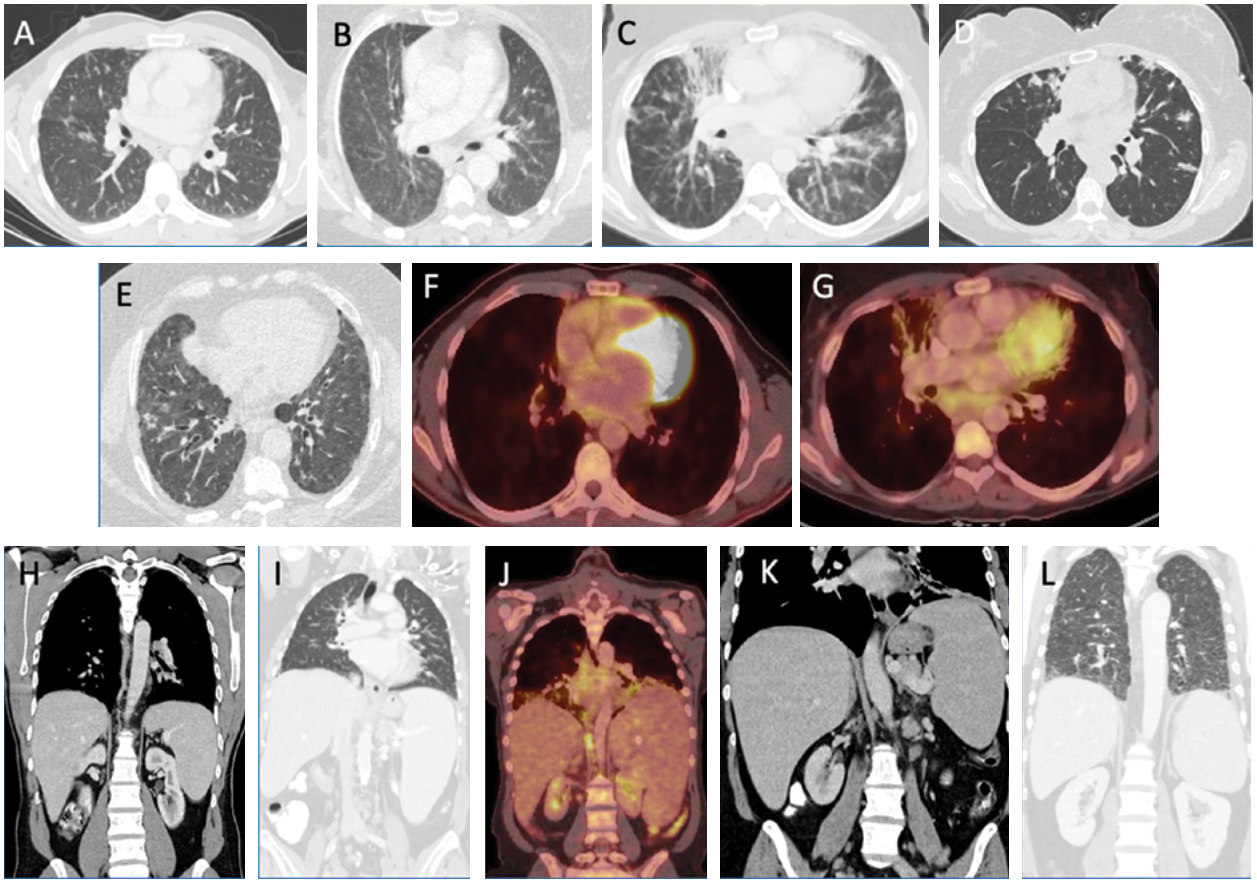
cytes and plasma cells, without granulomas or clonality. Additional imaging showed diffuse lymphadenopathy and splenomegaly (19 cm) [Figure 1I]. A recent immune workup revealed significant hypogammaglobulinemia with IgG of 361 mg/dl (and evidence for low total protein approximately 13 years prior). PFTs showed restrictive pattern with forced expiratory volume in 1 second (FEV1) of 54% and FEV1/forced vital capacity (FVC) ratio of 0.91. The patient is treated with IgRT and awaiting rituximab treatment.

Patient 3

A 57-year-old female with a remote history of immune thrombocytopenia at the age of 23 years was evaluated for a chronic cough and dyspnea. Immune workup showed low antibody levels with IgG of 375 mg/dl and the patient was started on IgRT. Imaging studies showed diffuse lymphadenopathy and hepatosplenomegaly (with a spleen of 25 cm) [Figure 1J]. Chest imaging revealed bilateral infiltrates, numerous nodules, and bronchiectasis [Figure 1C, 1G]. A lung biopsy showed a mixed population of small T and B lymphocytes, with a high number of B cells, and no clonality. PFTs showed a restrictive pattern with FEV1 of 52%, FEV1/FVC ratio of 0.70, impaired diffusion capacity with diffusing capacity of the lungs for carbon monoxide (DLCO) of 41%, and low six-minute walk test (6MWT) of 311 meters (normal range 400–700) with post challenge desaturation of 88%. Systemic steroids were initiated and rituximab treatment was considered.

Figure 1. Chest and abdominal imaging

[A-G] Show different patterns of lung involvement with reticular changes, infiltrates and lung nodules
[F and G] Show diffusely increased FDG uptake in lung fields
[A and F] Patient 1 **[B]** Patient 2 **[C and G]** Patient 3 **[D]** Patient 4 **[E]** Patient 5
[H-L] Show significant splenomegaly in all 5 patients **[H]** Patient 1 **[I]** Patient 2 **[J]** Patient 3 **[K]** Patient 4 **[L]** Patient 5



Patient 4

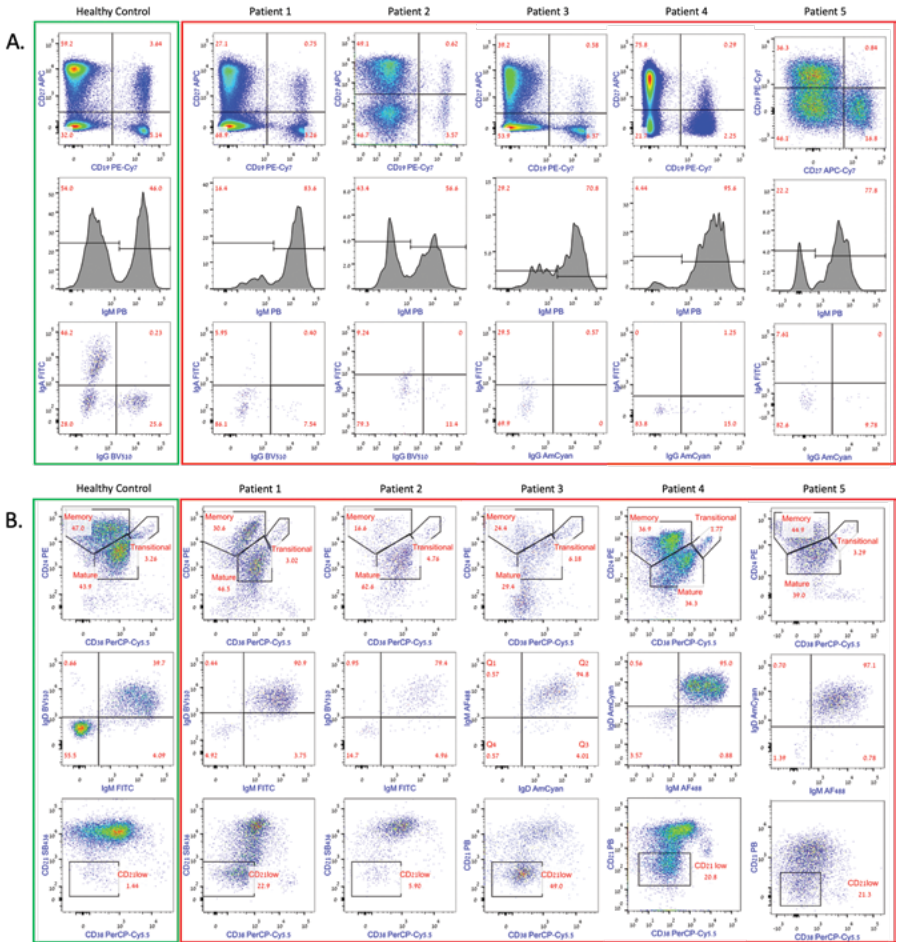
A 49-year-old female was diagnosed with CVID at the age of 27 years, presenting with recurrent pneumonias and significantly reduced IgG levels of approximately 200 mg/dl. Imaging studies at the time of diagnosis showed diffuse lymphadenopathy with biopsy suggesting reactive lymph-node. Chest imaging at the time revealed significant bilateral bronchiectasis. Around the age of 45 years the patient started presenting more frequent respiratory symptoms. Repeated imaging showed multiple bilateral lung nodules in addition to bronchiectasis [Figure 1D] and hepato-splenomegaly (liver of 22 cm and spleen of 16 cm) [Figure 1K]. A lung biopsy showed extensive lymphocytic infiltrates, staining positive for both CD3 and CD20, without granulomas and no evidence for clonality. PFTs showed mild impairment with FEV1 of 70.5%, ratio of 0.76, and DLCO of 61%. The patient was treated with IgRT and prophylactic antibiotics.

Patient 5

A 32-year-old male with genetically confirmed Kabuki syndrome who first presented at the age of 12 years with ITP, responded well to IVIg and steroid treatment. He was asymptomatic for several years. At the age of

Figure 2. B-cell immunophenotyping

Green boxes show healthy control sample
Red boxes show patient samples
[A upper panels] B-cell immunophenotyping showed low percent of CD27^{+} CD19 cells
[A middle panels] Tendency toward low IgM class switching within the CD27^{+} cells
[A lower panels] Near absent IgA/IgG class switching
[B] Flowcytometry B-cell maturation panel
[B upper panels] Variability in the maturation into CD38^{low}CD24^{high} memory B cells
[B middle panels] Memory cells failed to show significant class switching, with nearly no IgM/IgD double negative cells
[B lower panels] Staining for CD21, showed significantly elevated CD21low population of more than 20% in 4 of the 5 GLILD patients



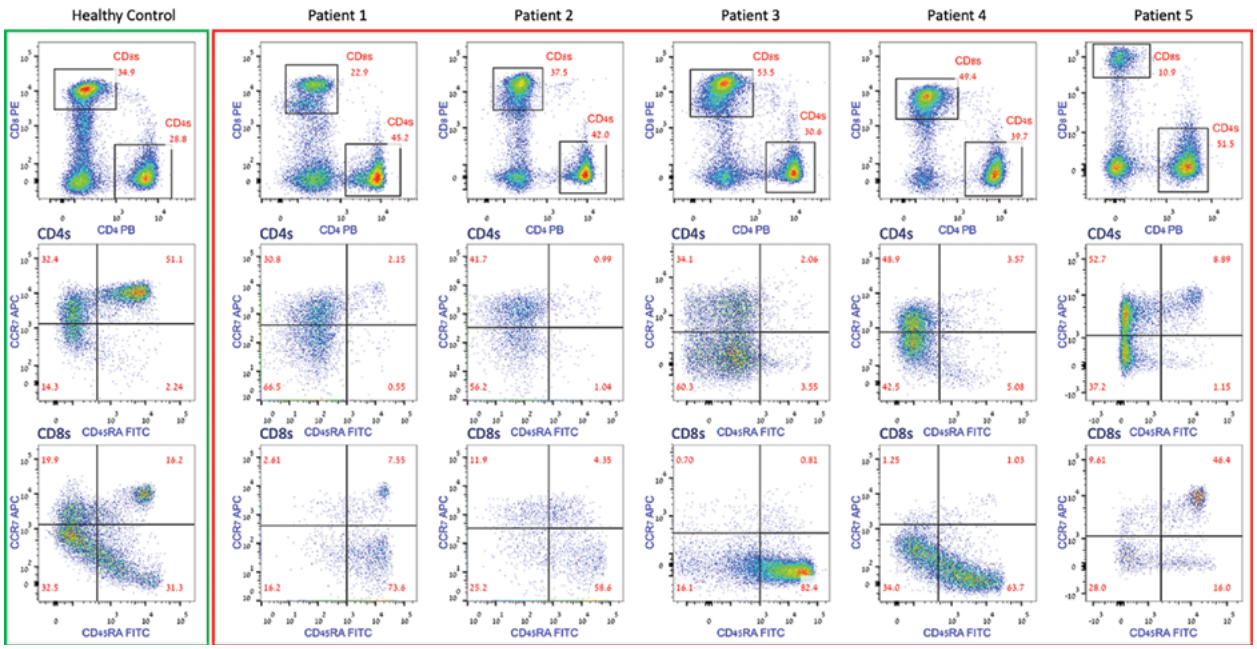
27 years he developed autoimmune hemolytic anemia. At that time, he reported presenting with several years of episodic dyspnea. Chest imaging showed numerous bilateral lung nodules and patterns of interstitial lung disease [Figure 1F]. PFTs showed restrictive pattern with FEV1 of 37.6% and a ratio of 0.85 as well as significantly reduced corrected diffusion capacity of 65%. Immune workup at that time showed low antibody levels with IgG of 319 mg/dl, and additional imaging revealed mediastinal lymphadenopathy and splenomegaly (16 cm) [Figure 1L]. The patient started on high dose steroids and IgRT. Over the next several years the patient developed progressive dyspnea and a chronic productive cough. Repeated PFTs showed restrictive pattern with FEV1 of 36% with ratio of 0.88, and low 6MWT distance of 300 meters (53% of predicted) with post challenge desaturation of 85%. Based on a probable diagnosis of GLILD, the patient was treated with six weekly doses of rituximab (375 mg/m^2) with partial improvement, reflected by an increase in FEV1 from 36% to 48%, and improvement in 6MWT distance from 300 meters [53%] to 392 meters [71%]. The patient repeated courses of rituximab.

B-CELL AND T-CELL IMMUNOPHENOTYPING

B-cell immunophenotyping performed as part of routine evaluation of suspected CVID patients showed a similar pattern shared by all four GLILD patients who were tested. All five patients had a low percentage of CD27$^+$ memory CD19$^+$ B cells, with significantly impaired class switching reflected by nearly absent CD27$^+$IgM$^-$ IgA$^+$ or IgG$^+$ B-cells [Figure 2 upper panels]. They also showed near absent class-switched (IgM/IgD double negative) CD38^{low}CD24^{high} memory B cells [Figure 2 lower panels]. In addition, four of the five tested patients had significantly high percent of CD21low B cells of above 20% [Figure 2 lower panels]. This pattern of profoundly impaired class-switching and significantly increased CD21low B cells was observed even when compared with twelve adult CVID patients who did not show evidence for autoimmunity or immune dysregulation (CVID, infection only). As such, the average percent of CD27+IgM- IgA+ or CD27+IgM-IgG+ was 4.56% ± 4.32 and 8.74% ± 5.69 in GLILD patients, vs. 24.57% ± 19.69 and 31.22% ± 16.52 in the CVID-infection only group (P = 0.043 and P = 0.0085, respectively). Similarly, the average percent of class-switched IgM/IgD double negative CD38lowC-

Figure 3. T-cell immunophenotyping

T-cell immunophenotyping shows abnormal maturation of both CD4 and CD8 T-cells. Middle panels show gating on the CD4$^+$ cells. While all three CD4 subpopulations (naïve, central memory, and effector memory) can be seen in the healthy control sample (green), all four patients (red) showed low to near absent naïve CD45RA/CCR7 double positive cells. Gating on CD8$^+$ cells (lower panels) showed similar pattern of low naïve cells in 4 of 5 patients.



D24high memory B cells was 5.03% ± 5.67 in GLILD patients vs. 17.85% ± 12.59 in the CVID-infection only group ($P = 0.047$). Finally, the average percent of the CD-21low B cells was 23.98% ± 15.58 in GLILD, vs. 5.61% ± 5.96 in the CVID control group $P = 0.0036$).

T-cell immunophenotyping also demonstrated shared abnormal maturation pattern, most significant for low to absent $CD45RA^+CCR7^+$ naïve $CD4^+$ T cells in all five patients [Figure 3 middle panels] and low to absent naïve $CD8^+$ T cells in four of the five patients [Figure 3 lower panels]. This result is consistent with previous study of 23 GLILD CVID patients [12]. This impaired maturation pattern was more profound when compared with six adult CVID infection-only patients, with an average percent of naïve CD4 T cells of 3.53% ± 3.13 in GLILD patients vs. 40.66% ± 17.88 in CVID-infection only ($P = 0.0014$), and tendency toward lower percent of naïve CD8 T cells with an average of 12.08% ± 19.41 in GLILD patients, vs 28.46% ± 20.69 in CVID controls ($P = 0.21$).

DISCUSSION

CVID, a predominantly antibody deficiency syndrome, is often considered as an immunodeficiency disorder, causing susceptibility to recurrent bacterial infections, affecting mostly the respiratory system (recurrent sinopulmonary infections). However, numerous studies have emphasized the immune dysregulation aspect of the disease, with a high incidence of autoimmunity, autoinflammation, and/or lymphoproliferation. As such, CVID should be considered as a multisystem disorder, involving different organ systems, with the potential of causing end-organ damage and affecting overall well-being and survival.

The lungs are one of the more commonly involved organs, either due to direct damage caused by frequent and recurrent infections (bronchiectasis), or as the result of dysregulated immune response with the development of interstitial lung disease (ILD) [13]. Of the different forms of ILDs, GLILD is the most described, and was shown to be associated with significant morbidity and increased risk of mortality [14]. The diagnosis of GLILD requires a combination of typical radiologic and pathologic findings, together with clinical evaluation which include complete pulmonary function tests and diffusion capacity.

We described small cohort of five CVID GLILD patients and highlighted several points. First, there is no timeline for the development of GLILD, as GLILD can develop after years of stable disease [Table 1] (patients 2, 4, and 5) or be the initial presenting symptom (patients 1 and 3). In addition, GLILD is associated with lymphadenopathy and splenomegaly (all 5 patients), as well as with immune cytopenias (3 of 5), but without gastrointestinal involvement, as shown in Table 1. Similar findings of lymphoproliferation and absence of gastrointestinal disease were also described by Bintalib et al. [13]. Clinically, GLILD can cause significant lung impairment with the development of a severe restrictive pattern and reduced diffusion capacity (patients 2,3, and 5) or can be nearly asymptomatic (patient 1).

B-cell and T-cell immune phenotyping also showed several unique features, with severely impaired class-switching and a low percent of naïve CD4+ and CD8+ T cells, even when compared with other CVID patients who did not show evidence of immune dysregulation (CVID infection-only). This finding is in accordance with previous studies, which showed similar findings of impaired class-switching, increased CD21low B cells and low naïve T-cells in CVID-GLILD patients, with changes more profound compared with other (GLILD negative) CVIDs [12,13].

Treatment of GLILD is challenging and there are no large clinical studies to indicate effective treatment. Nevertheless, as lung biopsies often show lymphocytic infiltrates of both B cells and T cells, current practice supports the use of rituximab to eliminate infiltrating B cells, with or without the addition of T-cell targeted therapies, such as mycophenolate mofetil, azathioprine or abatacept [15]. The efficacy or rituximab monotherapy was demonstrated in one of the cohort patients (patient 5) who showed partial improvement in his PFTs and 6MWT. In addition, the use of rituximab alone is somewhat appealing, especially as most CVID GLILD patients are treated with IgRT, and as T-cell immunophenotyping shows reduced naïve T cells [16].

CONCLUSIONS

CVID is a complex and multi-system disorder, with the lungs being a major target organ. The fact that GLILD can develop at any stage and can be clinically silent for many years suggests that GLILD should be actively searched for in CVID patients at baseline, especially if the patient has splenomegaly, and if B cell and T cell immunophenotyping show significantly high percent of CD21low B cells, and very low to near absent naïve CD4 and CD8 T cells. GLILD should also be searched for in case of development or worsening of respiratory symptoms. While the correct timing of initiating treatment is unknown, early identification could trigger early treatment, thus preventing irreversible lung damage.

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References

1. Kindle G, Alligon M, Albert MH, et al; ESID Registry Working Party. Inborn errors of immunity: Manifestation, treatment, and outcome-an ESID registry 1994-2024 report on 30,628 patients. *J Hum Immun* 2025; 1 (3): e20250007.
2. Tobin JM, Cooper MA. Rheumatologic and autoimmune features of inborn errors of immunity: implications for diagnosis and management. *J Hum Immun* 2025; 1 (3): e20250034.
3. Bonilla FA, Barlan I, Chapel H, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract* 2016; 4 (1): 38-59.
4. Gathmann B, Mahlaoui N, CEREDIH, et al; European Society for Immunodeficiencies Registry Working Party. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2014; 134 (1): 116-26.
5. Seidel MG, Kindle G, Gathmann B, et al; ESID Registry Working Party and collaborators. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. *J Allergy Clin Immunol Pract* 2019; 7 (6): 1763-70.
6. Cunningham-Rundles C, Casanova JL, Boisson B. Genetics and clinical phenotypes in common variable immunodeficiency. *Front Genet* 2024; 14: 1272912.
7. Tangye SG, Nguyen T, Deenick EK, Bryant VL, Ma CS. Inborn errors of human B cell development, differentiation, and function. *J Exp Med* 2023; 220 (7): e20221105.
8. Ameratunga R, Edwards ESJ, Lehnert K, et al. The rapidly expanding genetic spectrum of common variable immunodeficiency-like disorders. *J Allergy Clin Immunol Pract* 2023; 11 (6): 1646-64.
9. Ho HE, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: updated clinical spectrum, sequelae, and insights to pathogenesis. *Front Immunol* 2020; 11: 149.
10. Ducasa GM, Marsh RA, Mojebi A, et al. A systematic literature review of CVID reveals pervasive detrimental noninfectious manifestations. *J Hum Immun* 2025; 2 (1): e20250157.
11. Hurst JR, Verma N, Lowe D, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract* 2017; 5 (4): 938-45.
12. Lui VG, Ghosh T, Rymaszewski A, et al. Dysregulated lymphocyte antigen receptor signaling in common variable immunodeficiency with granulomatous lymphocytic interstitial lung disease. *J Clin Immunol* 2023; 43 (6): 1311-25.
13. Bintalib HM, Grigoriadou S, Patel SY, et al. Investigating pulmonary and non-infectious complications in common variable immunodeficiency disorders: a UK national multi-centre study. *Front Immunol* 2024; 15: 1451813.
14. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J Allergy Clin Immunol* 2004; 114 (2): 415-21.
15. Lamers OAC, Smits BM, Leavis HL, et al. Treatment strategies for GLILD in common variable immunodeficiency: a systematic review. *Front Immunol* 2021; 12: 606099.
16. Pecoraro A, Crescenzi L, Galdiero MR, et al. Immunosuppressive therapy with rituximab in common variable immunodeficiency. *Clin Mol Allergy* 2019; 17: 9.

Capsule

Clues in early immune responses to tuberculosis

Most people who are infected with *Mycobacterium tuberculosis* do not progress to active disease. **Branchett** and colleagues used single-cell sequencing approaches to profile immune cells in the lungs of individuals who were recent household contacts for patients with tuberculosis. Contacts who went on to develop tuberculosis exhibited elevated neutrophils and dysfunctional T cells in the lung. By contrast, the immune responses in people who did not progress toward disease were dominated by protective T cells with a quiescent or stem-like state. These findings indicate that the early immune response of an individual to *M. tuberculosis* may dictate the outcome of the infection.

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Eitan Israeli

Capsule

Lethal combinations with NDRG1

DNA damage repair is essential to cell survival, making it an attractive target for cancer therapy. Using high-throughput screens, **Mkrtchyan** and co-authors identified a therapeutically exploitable role for the scaffolding protein *NDRG1* in the DNA damage response. High *NDRG1* expression in cancer cells correlated with sensitivity to the antimalarial drug quinacrine, which impaired the ubiquitylation-dependent recruitment of a critical protein to sites of DNA damage. Colorectal cancer cells with mutations in two DNA repair-associated genes were particularly sensitive to quinacrine or *NDRG1* loss. These findings suggest that therapy may be informed by *NDRG1* expression.

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