

Autoimmune Hemolytic Anemia and Spontaneous Pneumothorax as Initial Manifestations of Common Variable Immunodeficiency Complicated with Granulomatous-Lymphocytic Interstitial Lung Disease

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ABSTRACT

Common variable immunodeficiency (CVID) is the most common antibody deficiency in adults and is frequently associated with autoimmune conditions. One such condition is autoimmune hemolytic anemia (AIHA), an acquired blood disorder that can be the initial manifestation of CVID. Additionally, patients may develop granulomatous and lymphoproliferative lung disease (GLILD), a serious complication that worsens prognosis and requires early recognition. We describe a 25-year-old man with AIHA who had a severe hemolytic crisis and persistent anemia despite optimal immunomodulatory therapy. Infectious diseases, other autoimmune disorders and neoplasms were ruled out. In further studies, marked hypogammaglobulinemia of IgG, IgA, IgM and IgE was documented, confirming the diagnosis of CVID as the underlying cause of his refractory AIHA. During hospitalization, the patient developed a spontaneous pneumothorax with associated pulmonary micronodules, raising a strong suspicion of GLILD. This case illustrates that CVID may initially present as apparently isolated AIHA and remain unrecognized until serious complications emerge. Measurement of serum immunoglobulin levels should be considered in patients with atypical or treatment-refractory AIHA, recurrent infections, or accompanying lymphoproliferative features, as early recognition of CVID enables timely IVIG replacement and monitoring for associated complications.

Keywords: Common variable immunodeficiency; Hemolytic anemia; Granulomatous lymphocytic interstitial lung disease; Autoimmune extra-pulmonary manifestations; Hematologic disease; Primary immunodeficiency

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is an acquired autoimmune blood disorder caused by the destruction of red blood cells due to autoantibodies. In adults, AIHA can be secondary to hematological

malignancies, infections, and autoimmune disorders, but it is often classified as idiopathic¹.

Common variable immunodeficiency (CVID) is an antibody deficiency characterized by low levels of immunoglobulins (IgG, IgA, and/or IgM), leading to frequent and severe infections. However, not all

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patients manifest with recurrent infections; many develop autoimmune, inflammatory, or lymphoproliferative complications, including hematologic malignancies. CVID is the most common symptomatic adult-onset inborn error of immunity affecting antibody production and is clinically heterogeneous. About one-quarter of patients with CVID experience autoimmune events, including immune thrombocytopenia, AIHA, autoimmune thyroiditis, vitiligo, pernicious anemia, rheumatoid arthritis, or vasculitis^{2-4,10,13}. In CVID, defective B-cell maturation and class-switch recombination impair humoral immunity and disrupt central and peripheral tolerance, favoring survival of autoreactive clones that can mediate autoimmune cytopenias such as AIHA^{4,10}. In parallel, broader immune dysregulation (abnormal T-cell help, reduced regulatory T-cell function, and expansion of activated/atypical B-cell subsets) contributes to loss of immune tolerance and autoimmune cytopenias^{4,10,13}.

An uncommon but potentially fatal complication of CVID is granulomatous-lymphocytic interstitial lung disease (GLILD), a distinct clinico-radiologic-pathologic ILD that reflects immune dysregulation and is associated with a worse prognosis^{5,7,15}. Mechanistically, abnormalities in T-cell regulation, dysregulated cytokine signaling, and impaired clearance of apoptotic material may contribute to chronic immune activation and granulomatous/lymphoproliferative inflammation in the lung^{5,15}.

Some patients with CVID initially manifest autoimmunity for years, while infections emerge later, once the progressive humoral defect and cumulative tissue damage exceed the compensatory capacity of the residual immune response⁷. High clinical suspicion is crucial for an accurate diagnosis⁷. We describe the case of a patient with CVID complicated by GLILD, who presented with hemolytic anemia and spontaneous pneumothorax.

Case presentation

A 25-year-old male, mestizo patient with a personal history of warm autoimmune hemolytic anemia (wAIHA) diagnosed 2 years prior this evaluation non adherent to medical treatment presented to a third

level Hospital in Cali, Colombia. He consulted for 1-week asthenia, mucocutaneous jaundice and upper right abdominal pain. The review of systems revealed for 10 kg loss of weight in the past 8 months and appearance of bilateral inguinal lymph nodes studied with biopsy in another institution ruling out a lymphoproliferative disorder.

On his physical examination did not present hemodynamic instability, he was afebrile with scleral icterus and abdominal tenderness due to hepatosplenomegaly without signs of peritoneal irritation. In laboratory tests, complete blood count with severe regenerative normocytic normochromic anemia, normal platelets and white blood cell count associated with indirect hyperbilirubinemia and elevation of lactate dehydrogenase. Complete liver function tests, serum electrolytes, and renal function, were found in normal ranges. Fourth generation ELISA for HIV was negative other tests for infections as VDRL, HBV sAg, syphilis, and IgG anti HCC were also negative. Autoimmune diseases were excluded with negative results of antinuclear antibodies, extractable nuclear antigen, anti-DNA antibodies, rheumatoid factor, anticardiolipin IgG and IgM, anti-beta 2 glycoprotein IgG and IgM and lupus anticoagulant were negative. Due to normal C3 complement serum levels with C4 consumption, serum cryoglobulins were ordered and were negative. He had normal folic acid and vitamin B12 replacement therapy was started due to deficiency. In view of a hemolytic crisis, steroid pulses with methylprednisolone were started after deworming and immunomodulation therapy with azathioprine was restarted. However, due to the persistence of severe anemia requiring transfusion support; serum protein electrophoresis, serum immunofixation, and serum immunoglobulins were ordered, confirming hypogammaglobulinemia with decreased IgG levels of 358 mg/dL (reference range 700-1600 mg/dL), IgA <40 mg/dL (reference range 40-350 mg/dL), IgM <25 mg/dL (reference range 54-300 mg/dL) and IgE 90 mg/dL (reference range 100 mg/dL).

With these findings, it was necessary to rule out humoral immunodeficiency, since although it was initially considered to be secondary to the use of azathioprine and parenteral corticosteroid; immunoglobulin levels were re-evaluated 2 weeks

and 6 months later confirming the same findings. This interval reflected logistical difficulties in maintaining close follow-up, as the patient lived in a remote rural area.

Bone marrow aspiration and biopsy studies were conducted revealing normocellular (80%), erythroid hyperplasia with a series of neutrophils and monocytes without maturation alterations suggestive of myelodysplasia and with a normal immunophenotype. Lymphocytes showed expression of CD19, CD20, and absence of CD5. Surface light chains of a polyclonal B-lymphoid population (Kappa 71% - Lambda 29%). T lymphocytes were CD3+, CD5+, with a CD4:CD8 T-cell ratio of 0.78. Plasma cells accounted for 0.03% of the evaluated events.

According to the ESID Registry – Working Definitions for the Clinical Diagnosis of Primary Immunodeficiency (PID),⁽⁸⁾ a probable diagnosis of Common Variable Immunodeficiency (CVID) with autoimmune manifestations was established based on specific clinical criteria. These criteria included a significant decrease in IgG and IgA levels, along with low IgM levels, measured on at least two occasions with a 6-month interval and falling below 2 standard deviations (SD) of normal levels for the patient's age. He had a Group O positive blood type, and isohemagglutinins were found to be absent (0/++++). Secondary causes of hypogammaglobulinemia were excluded, and there was no evidence of severe T-cell deficiency, as indicated by CD4+ at 521/mm³ and CD8 at 320/mm³. The diagnosis of CVID was made, sequence of events is summarized in the clinical timeline (Figure 1).

Since the patient had described inguinal lymph nodes that resolved spontaneously, the possibility of immunodeficiency-associated lymphoproliferative disorders was latent. Computed Tomography (CT) scan of neck, thorax, abdomen and pelvis with contrast was requested, which found hepatosplenomegaly without infiltrative lesions. However chest CT (Figure 2) showed diffuse interstitial infiltrates involving both lungs, predominantly in the lower lobes with solid micronodules, the largest subpleural 1.2 cm in the left upper lobe and axillary lymph nodes. At that

time, it was proposed to carry out studies to detect infections and radiological follow-up after a month. During the hospital stay, despite being respiratory asymptomatic, a new control chest CT scan (Figure 2) was performed, where incidentally a 100% right spontaneous pneumothorax was found with atelectasis of the lower and middle lobe. He was taken to a closed pigtail thoracostomy, which was later withdrawn after respiratory incentive and adequate lung re-expansion (Figure 2). Once the patient was stabilized, fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) was performed to rule out infections (bacteria, mycobacteria, and fungi), all negative. The differential cell count using standard cytology and flow cytometry in BAL showed 95% macrophages and 5% lymphocytes, without polymorphonuclear cells or atypical cells. Although BAL in GLILD is often lymphocyte-predominant, BAL findings are variable and non-diagnostic; in this case, the working diagnosis was driven by the CVID background, characteristic HRCT pattern (lower-lobe predominant interstitial infiltrates with multiple small subpleural nodules and lymphadenopathy), and exclusion of infectious or malignant causes^{7,15}. Transbronchial biopsy showed thickened septa with abundant lymphoplasmacytic interstitial inflammation (Figure 3). No granulomas or neoplasia were observed; given the known histopathologic heterogeneity of GLILD and sampling limitations of transbronchial biopsies, the overall clinico-radiologic picture remained most consistent with probable GLILD^{7,15,17}.

Due to the pulmonary radiological findings and the BAL studies in the context of the patient with CVID, a working diagnosis of probable granulomatous-lymphocytic interstitial lung disease (GLILD) was made^{7,15}. For this reason, in addition to chronic replacement with intravenous immunoglobulin at a monthly dose of 0.4 grams/kg, it was decided to start anti-CD20 therapy and monthly monitoring of IgG. In follow-up at 6 months by hematology, with no new hospitalizations for hemolytic crises, the patient continues to exhibit hypogammaglobulinemia due to irregular administration of IVIG caused by delivery difficulties. Whole exome sequencing focused on genes associated with Inborn Errors of Immunity was

requested. As of this report, administrative approval for the sequencing is still pending.

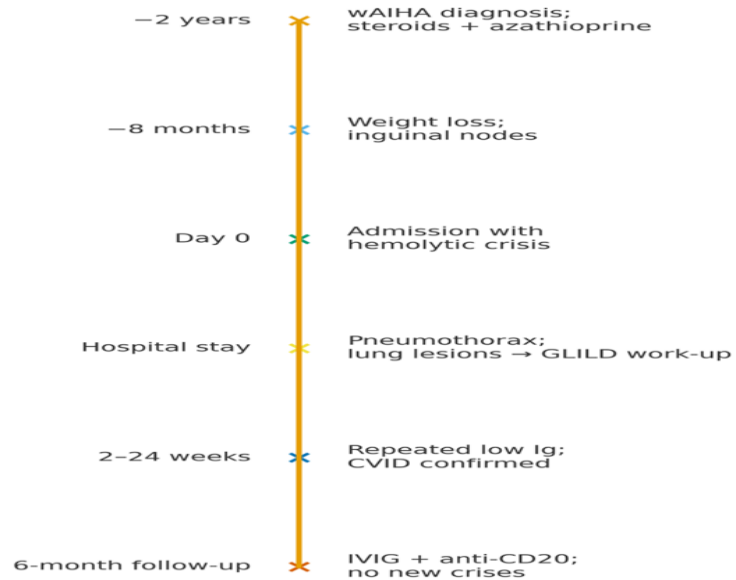


Figure 1. Clinical timeline of the patient. Key milestones from initial wAIHA diagnosis to CVID/GLILD confirmation and 6-month follow-up after IVIG and anti-CD20 therapy are shown chronologically

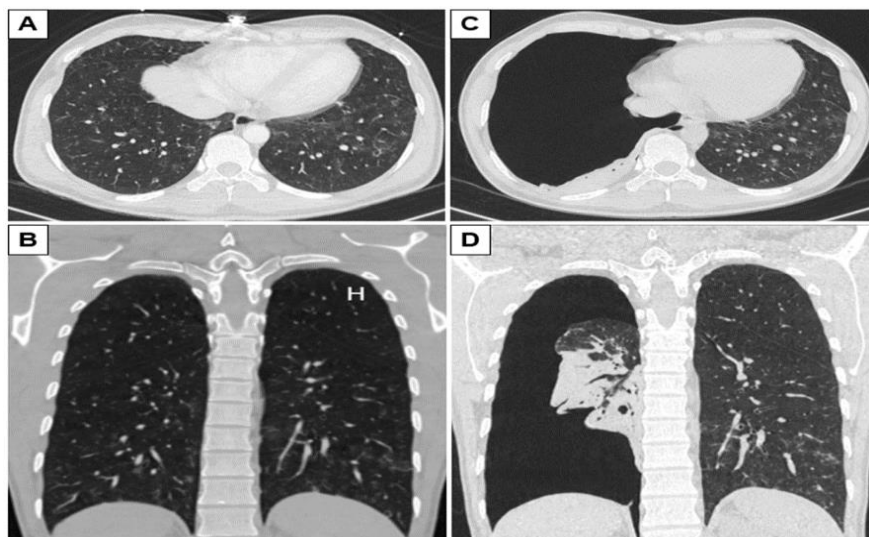


Figure 2. (A, B): Thorax CT. Diffuse interstitial infiltrates involving both lung fields, mainly in the lower lobes, associated with micronodular lesions and axillary lymphadenopathy; (C, D): Thorax CT. Spontaneous pneumothorax

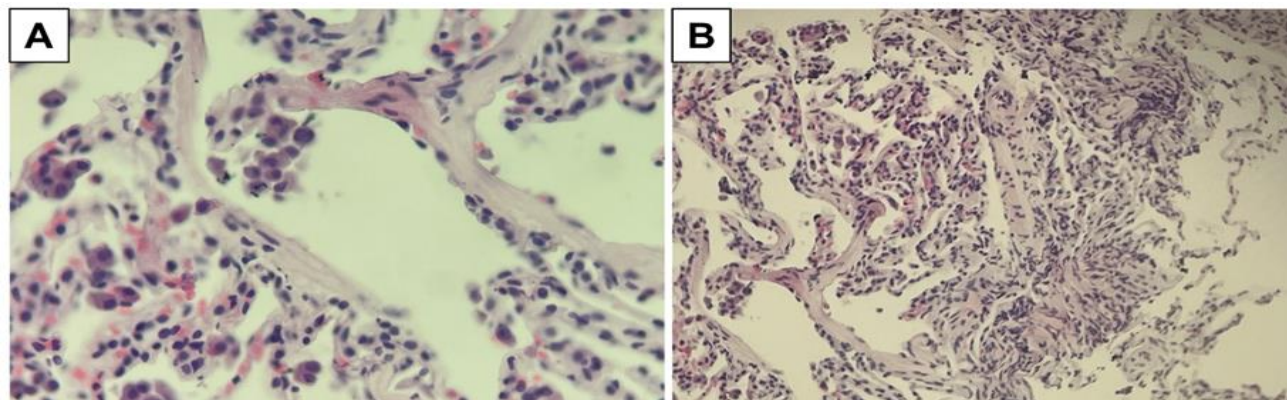


Figure 3. A) Histologic section of lung parenchyma showing markedly thickened alveolar septa with a dense lymphoplasmacytic infiltrate; no granulomas, necrosis, or neoplastic cells are identified, in keeping with chronic interstitial inflammation. B) Higher-power view demonstrating that the inflammatory infiltrate is composed predominantly of macrophages and lymphocytes, with minimal neutrophils, supporting a chronic, non-suppurative pattern compatible with GLILD in the context of CVID.

DISCUSSION

Common variable immunodeficiency (CVID) is an immune disorder that includes patients with hypogammaglobulinemia and presents with a variable phenotype. The diagnosis of CVID is based on defined criteria according to the ESID Registry - Working Definitions for Clinical Diagnosis of PID. A patient may develop increased susceptibility to infections, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or have a family member affected by antibody deficiency. It must include: (1) A marked decrease in IgG levels (at least two standard deviations below the mean for age, measured at least twice) and of at least one of the IgM or IgA isotypes; (2) onset of immunodeficiency at greater than 4 years of age; and (3) absence of isohemagglutinins and/or poor response to vaccines and/or low switched memory B cells; and (4) no evidence of profound T-cell deficiency. However, other causes of hypogammaglobulinemia must be excluded. Although most patients present with IgG levels below 400 mg/dL, as in our case, some authors recommend initiating immunoglobulin replacement when levels fall below 200 mg/dL, even without confirmatory functional studies, given the increased risk of pneumonia. Our patient had hypogammaglobulinemia of IgG, IgM, IgA, and IgE. Initially, we considered that it could be secondary to steroid pulse therapy, but previous studies have

shown that IgM and IgA levels are not usually diminished by corticosteroids. Nevertheless, during follow-up, two weeks and six months after discontinuation of immunomodulation, serum immunoglobulin levels remained low and absent isohemagglutinins. This highlights the importance of checking immunoglobulin levels before starting immunomodulation in autoimmune diseases to avoid biases.

Approximately 20–22% of patients with CVID develop autoimmune disease, most frequently immune thrombocytopenia (ITP) or autoimmune hemolytic anemia (AIHA)^{12,13}. In published cohorts, AIHA may precede the diagnosis of CVID by several years, contributing to delayed recognition and preventable complications¹². This reflects the immune dysregulation intrinsic to CVID, where autoimmunity may be the first clinical signal rather than recurrent infection. Accordingly, adults presenting with atypical or treatment-refractory autoimmune cytopenias should prompt evaluation for underlying inborn errors of immunity, including measurement of serum immunoglobulins^{8,12,13}.

CVID patients may develop granulomatous-lymphocytic interstitial lung disease (GLILD), reported in approximately 8–22% of cases and associated with increased morbidity and mortality^{7,15}. GLILD typically occurs in a multisystem immunoregulatory context and is frequently

accompanied by lymphadenopathy and splenomegaly, reinforcing its lymphoproliferative phenotype^{7,15}. On high-resolution CT (HRCT), common patterns include lower-lung predominant ground-glass opacities and consolidation (often reflecting organizing pneumonia), scattered nodules/micronodules, bronchiectasis, and reticulation or fibrotic change^{7,15,16}. In our patient, thorax CT demonstrated diffuse interstitial infiltrates with lower-lobe predominance, multiple small solid subpleural nodules, and adenopathy, which—together with hypogammaglobulinemia and systemic lymphoproliferation—supported a GLILD phenotype^{7,15}.

Transbronchial biopsy (TBB) revealed thickened septa with dense lymphoplasmacytic interstitial inflammation without granulomas or neoplasia (Figure 3). This pattern is compatible with the histopathologic spectrum of GLILD, which can include lymphoid interstitial pneumonia, follicular bronchiolitis, organizing pneumonia, and non-necrotizing granulomas in variable combinations; therefore, absence of granulomas on small biopsies does not exclude GLILD^{7,15,17}. Sampling limitations are particularly relevant because GLILD is often patchy, and transbronchial specimens may not capture granulomatous foci or the full architectural pattern⁷. In addition, our BAL showed macrophage predominance rather than the more typical lymphocytic pattern; however, BAL is not diagnostic for GLILD and must be interpreted within the broader clinical and radiologic context^{7,15}. Alternative diagnoses considered included atypical infection, hypersensitivity pneumonitis, sarcoid-like disease, organizing pneumonia without GLILD, and CVID-associated lymphoma. In our patient, extensive negative microbiology, bone marrow and imaging evaluation without evidence of malignancy, systemic lymphoproliferation (adenopathy and hepatosplenomegaly), and an HRCT pattern consistent with GLILD favored probable GLILD as the most unifying diagnosis^{7,15}.

The occurrence of spontaneous pneumothorax is a rare and instructive complication in CVID-associated ILD. We found no radiologic evidence of subpleural cysts or macroscopic bullous disease on serial chest CT scans; the predominant findings were diffuse

interstitial infiltrates with small solid subpleural micronodules. We interpret the pneumothorax as potentially related to chronic subpleural inflammatory injury, pleural fragility, and traction-related stress from evolving architectural distortion. Microscopic subpleural cystic changes may also rupture even when not apparent on CT. Air-leak complications such as pneumomediastinum have been reported in GLILD, supporting biological plausibility for spontaneous pleural rupture in this setting¹⁹.

Other infectious and malignant causes were considered and excluded. Pulmonary function tests (PFTs) could not be performed due to the recent pneumothorax. Given the rarity of pneumothorax as a presenting complication of GLILD, this case underscores the need for vigilance for air-leak syndromes in CVID-associated ILD, particularly when there is a subpleural inflammatory burden. Treatment strategies for GLILD remain heterogeneous and largely evidence-limited. Systemic corticosteroids are commonly used for induction and can improve symptoms, lung function, and HRCT abnormalities, but relapses and steroid toxicity frequently necessitate steroid-sparing approaches^{7,15,20}. In reviews and small cohorts, B-cell depletion with rituximab—often combined with an antimetabolite—has been used as a steroid-sparing option, particularly when GLILD coexists with autoimmune cytopenias¹⁵. In our patient, rituximab was initiated to simultaneously control refractory AIHA and probable GLILD, balancing the need to control life-threatening autoimmune activity and lung disease against the additional infectious risk inherent to B-cell depletion in CVID. Risk mitigation included ongoing immunoglobulin replacement, planned IgG monitoring, and close clinical surveillance for infection^{15,18}.

Functional antibody testing (vaccine response assessment) and detailed memory B-cell phenotyping were not available in our setting, which limited further immunologic characterization of this case. As a result, the diagnosis of CVID rested on clinical features and serum immunoglobulin levels fulfilling ESID criteria rather than on advanced functional or phenotypic assays.

Table 1: Key hematologic and immunologic parameters at admission, during hospitalization, and at 6-month follow-up

Parameter	Day 1	Day 13	Day 26	6 months
Hemoglobin (g/dL)	5.3	8.4	11.5	15.10
WBC (cells/ μ L)	6910	6600	4160	5810.00
Platelets ($\times 10^3/\mu$ L)	201	227	202	226.00
Total bilirubin (mg/dL)	14.5	3.1	1.0	2.15
LDH (U/L)	338	186	148	232.00
IgA (mg/dL)	NA	NA	<40	44.00
IgG (mg/dL)	NA	303.34	462.84	472.00
IgM (mg/dL)	NA	NA	39.44	33.00
IgE (IU/mL)	NA	NA	0.5	0.12

CONCLUSION

This case highlights that assessing humoral immunity, including serum immunoglobulin levels, may be useful in patients with autoimmune hemolytic anemia (AIHA), particularly when the presentation is atypical or treatment-refractory. While a single report cannot justify a universal recommendation, our findings support considering underlying common variable immunodeficiency (CVID), as its early recognition can enable timely IVIG replacement and closer monitoring for associated complications.

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Right to privacy and informed consent

The authors have obtained the written informed consent from the mother and the assent from the patient mentioned in the article. The corresponding author is in possession of this document.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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