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CASE REPORT

Pulmonary involvement with immunodeficiency: the role of CTLA-4 in the pathogenesis of granulomatous lymphocytic interstitial lung disease (GLILD) - an Italian case report

The role of CTLA-4 in the pathogenesis of GLILD - an Italian case report

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ABSTRACT
We present the case of a 14-year-old female patient who was referred to us in 2024 due to coughing, widespread dermatitis and frequent episodes of diarrhea. Her medical history included atopic dermatitis in childhood. Initial blood tests and diagnostic tests revealed autoimmune hemolytic anemia, widespread lymphadenopathy and splenomegaly. Further diagnostic investigations revealed rounded pulmonary opacities on chest X-ray, so second-level diagnostic tests were performed, which revealed the presence of a mutation in the CTLA-4 gene on genetic analysis, suggesting a form of primary immunodeficiency, leading to a diagnosis of GLILD. Treatment initially involved corticosteroid therapy and the administration of intravenous immunoglobulins. The therapeutic breakthrough came with the introduction of biological therapy with Abatacept, a CTLA-4 signal modulator, which led to remission of the disease.

IMPACT STATEMENT
This case highlights the importance of differential diagnosis and multidisciplinary collaboration in the management of GLILD, offering a superior strategy compared to traditional corticosteroid-based management. Early adoption of targeted biological interventions is essential to halt disease progression, preventing the development of irreversible pulmonary fibrosis and reducing treatment-related morbidity, thereby improving long-term survival and quality of life for patients with CVID or CVID-like disorders.

INTRODUCTION

GLILD is defined as a clinical-radiological-pathological entity characterized by the presence of granulomatous inflammation and/or lymphocytic infiltrates in the lung parenchyma (1). Histologically, it presents a spectrum of extremely heterogeneous lymphoproliferative patterns, including follicular bronchiolitis and lymphoid interstitial pneumonia (LIP), which are often associated with multisystem involvement such as splenomegaly and lymphadenopathy (2). The

precise pathogenic mechanisms driving this pulmonary lymphoproliferation remain only partially understood.
Recent advances in genetic screening have identified a subgroup of CVID or CVID-like disorder phenotypes caused by specific monogenic defects, including alterations in the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene. CTLA-4 acts as a key negative immune regulator that maintains self-tolerance by competing with the costimulatory receptor CD28 for ligands on antigen-presenting cells. By removing these ligands via transendocytosis, CTLA-4 effectively suppresses excessive T cell activation and proliferation (3)
Heterozygous germline mutations leading to CTLA-4 haploinsufficiency result in a complex syndrome of immune dysregulation where T-cell homeostasis is severely disrupted (3). In these patients, the lack of effective T-cell checkpoint control facilitates the accumulation of activated lymphocytes in various organs, with the lungs being a primary target. Consequently, GLILD has become one of the signature clinical features of CTLA-4 deficiency, representing the pulmonary manifestation of a broader, systemic lymphoproliferative process driven by uncontrolled T-cell signaling (2).
The granulomatous-lymphocytic interstitial lung disease (GLILD) is a particularly severe manifestation, occurring in approximately 8% to 30% of CVID patients. Common variable immunodeficiency (CVID) is the most frequent clinically significant primary immunodeficiency in adults, historically characterized by hypogammaglobulinemia and an increased susceptibility to recurrent infections (2).
The clinical characteristics of the disease are extremely variable and include a range of symptoms starting with asthenia and possibly associated with pulmonary symptoms such as coughing and dyspnea, although in some cases the disease may be asymptomatic.
The aim of this clinical case is to highlight how varied and subtle the symptoms of this condition can be and how a multidisciplinary approach is essential to reach a diagnosis.
The objective of the discussion of this case is to highlight how immune dysregulation can be closely associated with pulmonary diseases and should therefore always be taken into consideration in order to increase awareness of the existence of the disease and improve its clinical recognition, thereby optimizing diagnostic and therapeutic strategies for affected patients.

CASE PRESENTATION

We present the case of a 14-year-old female patient. Born at term following a normal pregnancy. Neuropsychomotor development was adequate. Atopic dermatitis reported in childhood. No previous surgery, no hospital admissions, no significant infectious episodes reported.

In October 2023, a gastroenterological evaluation was performed for diarrhea lasting about a year and dermatitis. Blood tests were performed and the results were normal. Stool culture and parasitological tests were negative, while a slight increase in fecal calprotectin was found (59 µg, normal value < 50) and the fecal occult blood test was positive in 3 samples.

To rule out chronic inflammatory bowel disease, an abdominal ultrasound with loop study was performed in November 2023, revealing the following findings: Spleen 12 cm at upper limits (vn < 12cm), liver and bile ducts normal, no thickening of the last ileal loop.

In May 2024, the patient underwent a hematological assessment at our center to follow up on blood tests relating to autoimmune hemolytic anemia, which had been detected 20 days earlier but not subsequently confirmed. The examination revealed widespread lymphadenopathy, splenomegaly (stable compared to previous check); no weight loss.

Blood tests showed:

- Complete blood count: GB 7,700/mmc, Hb 8.8 g/dl, MCV 106.2 fl, PLT 295,000/mmc.
- Immunological tests: Coombs test: indirect/direct positive, presence of warm IgG antibodies, IgG 594 mg (slightly below normal), IgA 49 mg/dl, IgM 28 mg/dl. Blood group 0 Rh positive with anti-A and anti-B isohemagglutinins present; Tetanus antibodies doubtful.
- Various tests: Total bilirubin 2.15 mg/dl (indirect 1.44 mg/dl) LDH 669 U/L.
- Urine test normal and fecal occult blood negative; Calprotectin negative.

In October 2024, the patient was referred to us due to a dry, persistent cough, widespread dermatitis and frequent bouts of diarrhea. Respiratory function tests, such as spirometry and FeNo, were performed, with normal results.

To identify the cause of the cough more accurately, a chest X-ray was taken around 15 days later, revealing round opacities with a maximum projected diameter of approximately:

- 12 mm in the upper right field.
- 11 mm in the right basal area.
- 15 mm in the left basal area.

No pleural effusion. Cardio-mediastinal image within normal limits.

Suspecting a lymphoproliferative or metastatic process, advanced imaging tests were performed.

Second-level blood tests revealed hypogammaglobulinemia, with selective IgG2 deficiency: IgG2 38 (vn 106-610). Lymphocyte typing revealed humoral immune dysregulation.

To rule out an infectious cause, a number of serological tests were carried out on blood and stool samples, screening for the main potential infectious agents responsible for the condition, including EBV, CMV and parvovirus; all results were consistent with a previous infection.

In November 2024, due to persistent dermatitis, several skin biopsies were performed, which revealed spongiotic-eczematous dermatitis on histological examination.

From a hematological perspective, a bone marrow biopsy was also performed in November 2024, which revealed signs of macrocytosis and dyserythropoiesis, consistent with the hemolysis reported in the patient's medical history. Mild hyperplasia of megakaryocytes, of variable size, without significant atypia.

The lymphoid series consisted of cells with both T (CD3+) and B (CD20+) phenotypes, accounting for a total of approximately 15-20%, scattered throughout the interstitium and focally in centrilacunar follicular-type aggregates, likely reactive, to be correlated with the phenotypic data from flow cytometry. The bone marrow smear, on the other hand, revealed a hypercellular marrow with hyperplasia of the erythroid and megakaryocytic series, in the absence of morphological changes suggestive of MDS.

In December 2024, in order to investigate the radiological findings seen on chest X-ray, we performed a CT scan of the chest and mediastinum, which revealed lymphadenopathy in the hilo-mediastinal region, the largest and confluent in the subcarinal region – right hilar and para-aortic. Enlarged lymph nodes were also found in the lateral cervical region, the largest on the left

measuring approximately 2 × 1.3 cm. Multiple lymphadenopathy was found in the axillary region bilaterally, some rounded, with a maximum short axis of approximately 1.3 cm and smaller in the pectoral region.

Multiple bilateral central and peripheral parenchymal thickening, the most numerous and largest in the lower lobes (1.5 cm - 2 cm), in the basal segments of the LID tending to converge, but still widely recognizable, and some with a rounded morphology, these more evident in the LSD and LM.

It was not possible to perform a diagnostic bronchoscopy with bronchoalveolar lavage as the patient's parents refused the procedure due to its invasive nature.

To complete the diagnosis, the same month an MRI scan of the brain was also performed, which was normal, and a CT scan of the abdomen confirmed splenomegaly (bipolar diameter of approximately 15 cm), with minute parenchymal hypodensities, and lymphadenopathy of approximately 1 cm was reported in the perihilar hepatic region – interportal-caval region, also recognizable in the para-aorto-caval retroperitoneal region, in the mesenteric region and in the bilateral inguinal region.

In January 2025, as part of the diagnostic tests, a PET scan was also carried out, which described a hypermetabolic state in several mediastinal and extra-thoracic lymphnode districts and also highlighted numerous hypermetabolic areas with a nodular pattern in the lungs, with a prevalence in the lower lobes bilaterally. Areas of altered hyperperception were also described in other body regions such as the spleen, caecum, ascending colon, rectum, and last portion of the sigmoid colon.

In February 2025, we finally received the results of the genetic test, which revealed the presence of the NM_005214.5c.439A>G mutation in the CTLA-4 gene, suggesting a form of primary immunodeficiency, leading to a diagnosis of GLILD.

The patient's treatment initially involved the use of immunoglobulins due to her hypoglobulinemia, but this proved to be of little benefit. Oral steroid therapy was therefore initiated, resulting in partial clinical and radiological remission. The therapy we used was Prednisone at 1 mg/kg. Steroid therapy induced partial remission of the disease, with subsequent relapse, so we switched to a biological drug, Abatacept.

We opted to administer abatacept subcutaneously, at a dose of 125 mg per week, for a period determined by the patient's clinical response.

Its main role is as a targeted therapy for patients with specific genetic defects, particularly CTLA-4 or LRBA deficiency. The use of Abatacept allowed for a gradual reduction in oral steroid therapy, leading to a marked reduction in pulmonary thickening, until almost complete regression.

DISCUSSION

We present a clinical case of GLILD in a 14-year-old female patient with no suggestive clinical history of infections, significant respiratory symptoms and a negative family history of immunodeficiency.

The variant identified in our patient, who is responsible for the condition GLILD), is the CTLA-4 c.439A>G (NM_005214.5) variant is a recurrent pathogenic missense mutation that causes CTLA-4

haploinsufficiency, an autosomal dominant immune dysregulation syndrome with incomplete penetrance. Even within the same family carrying identical mutations, clinical manifestations vary dramatically from asymptomatic carriers to severe disease This mutation results in decreased CTLA-4 protein expression in regulatory T cells (Tregs), impaired transendocytosis of CD80/CD86 molecules, a key functional mechanism of CTLA-4. CTLA-4 haploinsufficiency causes a complex immune dysregulation syndrome characterized by both immunodeficiency and autoimmunity, which determines Hypogammaglobulinemia, Lymphoproliferation, autoimmune cytopenias, respiratory manifestations, such as recurrent infections, interstitial lung disease, lymphocytic infiltration. This condition can also lead to gastrointestinal and neurological involvement (9).

The diagnosis, clinical management and treatment of granulomatous lymphocytic interstitial lung disease (GLILD) represent one of the most significant challenges in the care of patients with common variable immunodeficiency (CVID) and non-CVID (4).

The management of infectious complications currently involves replacement therapy with immunoglobulins (IgRT) as a therapeutic strategy. The clinical manifestations that currently emerge as the primary causes of morbidity and reduced life expectancy are non-infectious manifestations caused by immune dysregulation (1-5).

A critical aspect of GLILD is its often insidious and asymptomatic onset (1). Symptoms, when present, are often non-specific, frequently manifesting as coughing and exertional dyspnea, and are not always correlated with the severity of lung parenchyma involvement, making the condition very difficult to diagnose (6).

The above is confirmed in the case of our patient, whose respiratory symptoms were very mild, manifesting only as a dry cough, with respiratory function tests, such as spirometry and FeNo, remaining consistently negative.

Diagnostically, High-Resolution Computed Tomography (HRCT) is the gold standard for detection, typically revealing a lower-lobe predominant pattern of nodules, ground-glass opacities, and interlobular septal thickening (2).

Respiratory function tests, on the other hand, could show a restrictive pattern with reduced DLCO in the presence of pulmonary manifestations.

Furthermore, GLILD should not be considered an isolated lung disease, but rather a component of a multisystemic lymphoproliferative process. The clinical manifestations of our patient are consistent with the literature, which suggests a strong correlation between GLILD and extrapulmonary features such as splenomegaly, generalized lymphadenopathy, and autoimmune cytopenia (7).

Perhaps the most interesting aspect of the clinical management of this disease is the recent possibility of introducing biological drugs. Initial treatment with immunoglobulins and oral corticosteroids may represent a first therapeutic approach, but it is often associated with relapses. The use of biological therapy with abatacept (CTLA-4-Ig) has become an innovative and fundamental strategy for patients with specific monogenic defects that overlap with the CVID phenotype, particularly CTLA-4 haploinsufficiency and LRBA deficiency (1). Abatacept acts as a soluble CTLA-4 mimic, binding these ligands and effectively suppressing excessive T-cell activation and proliferation.

In our case, the introduction of abatacept therapy enabled us to discontinue oral steroid treatment, resulting in a subjective clinical and radiological improvement.

CONCLUSIONS

In conclusion, the management of granulomatous-lymphocytic interstitial lung disease (GLILD) represents one of the most difficult clinical challenges, especially in the context of common variable immunodeficiency. As current evidence shows, this condition can no longer be considered an entity limited exclusively to the lung, but must be interpreted as the visible manifestation of a lymphoproliferative and multisystemic process driven by profound immune dysregulation. The wide clinical and radiological variability underscores the need for a multidisciplinary approach that integrates clinical, immunological and genetic data.

The future of treatment is moving away from the exclusive use of steroid therapy, which, although effective in inducing initial remission, is associated with frequent relapses. The introduction of biological therapies marks a decisive shift towards precision medicine. The use of rituximab in combination with antimetabolites has already demonstrated a superior ability to ensure lasting remissions and improve lung function compared to standard therapies. Even more promising is the use of targeted agents such as abatacept, which acts as a selective modulator of T cell co-stimulation, providing a great therapeutic alternative. Early identification of genetic and immunological biomarkers will be key to personalizing treatment. Personalized therapeutic management will therefore be useful in preventing irreversible parenchymal damage and fibrosis, significantly improving the survival and quality of life of patients affected by this disease.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

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Data sharing and data accessibility

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Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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