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WHEN LESS COULD BE MORE: SUCCESSFUL TREATMENT OF GRANULOMATOUS LYMPHOCYTIC INTERSTITIAL LUNG DISEASE WITH AZATHIOPRINE

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ABSTRACT

Introduction: Interstitial lung disease is a major complication in patients with common variable immunodeficiency. There are some publications that try to shed light on the pathophysiology of this non-infectious complication, most of them highlight the role of follicular T cells and CD21^{low} B cells. Moreover, there are no guidelines based on randomized controlled studies on the treatment of patients with interstitial lung disease and the published case series or small uncontrolled studies describe a wide range of response rates to treatment. In this scenario, the decisions are based on expert opinion rather than on robust scientific evidence. This could lead to potential biases associated with expert opinion based on a small number of patients.

Case description: We present the case of an adult patient with common variable immunodeficiency and interstitial lung disease. He did not receive rituximab due to an adverse reaction and underwent treatment with azathioprine, achieving prolonged remission after treatment discontinuation.

Discussion: If T-cell involvement could be the main underlying cause of this complication, treatment targeting T-cells may possibly be an effective therapeutic option. Our case, complemented with a physiopathology review, suggests a beneficial effect of azathioprine that warrants further research.

Conclusion: It is important to keep in mind that patients with common variable immunodeficiency are a heterogeneous group, so no single treatment will be the best for all of them. It is necessary to review the rationale for the increasing use of anti-CD20 drugs in non-infectious complications in patients with common variable immunodeficiency. Such use is based on expert recommendations and not on randomized, controlled studies with quantitative endpoints.

KEYWORDS

Common variable immunodeficiency, GLILD, interstitial lung disease, azathioprine, follicular T helper cells, CD21^{low} B cells

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LEARNING POINTS

- There are no guidelines based on randomized controlled studies on the treatment of patients with common variable immunodeficiency and interstitial lung disease.
- The use of rituximab in the treatment of various non-infectious manifestations in patients with common variable immunodeficiency, including interstitial lung disease, could be the result of potential biases associated with expert opinion based on a small number of patients.
- T-cell involvement could be the main underlying cause of this complication so treatment targeting T-cells may possibly be an effective therapeutic option.

INTRODUCTION/BACKGROUND

Patients with common variable immunodeficiency (CVID) can be classified based on their clinical phenotype according to whether they have non-infectious complications. This phenotypic distinction has important prognostic implications, as the risk of death is estimated to be 11 times higher in patients with non-infectious complications[1]. Interstitial lung disease (ILD) is one of the most frequent non-infectious manifestations, one of the main causes of morbidity and related to more than half of the deaths among CVID patients[2]. Since there are no guidelines based on randomized, controlled studies on the treatment of patients with ILD, deciding how to treat them is challenging. The evolution of one of our CVID-ILD patients led us to take a close look at why we chose certain drugs and to review the published evidence.

CASE DESCRIPTION

A 57-year-old male, who at age 25 had an episode of immune thrombocytopenic purpura with splenomegaly and 2 years later autoimmune haemolytic anaemia, both treated with glucocorticoids with good response. Five years later, he began to suffer recurrent infections and since age 38, he had chronic diarrhoea with lymphoid follicular hyperplasia findings on bowel biopsy. At 39 years of age, hypogammaglobulinemia was detected and he was diagnosed with CVID, initiating substitutive treatment with immunoglobulin. After he reached the age of 41, suggestive images of granulomatous-lymphocytic interstitial lung disease (GLILD), - nodules, ground glass opacities and mediastinal adenopathy - multiple lymphadenopathy and persistent splenomegaly were observed on positron emission tomography (PET-CT) scan. The biopsy of an axillary node showed lymphoid follicular hyperplasia whereas the pulmonary function tests were normal. At 42 years of age, due to a relapse of autoimmune haemolytic anaemia, he was treated with corticosteroids and rituximab with a favourable response.

Ten years later, he had cough, fever and weight loss, with normal pulmonary function tests. A PET-CT scan was performed which, in comparison with the previous one, showed increased metabolism of all known hypermetabolic images and increased size and metabolic enhancement in the pulmonary nodules *(Fig. 1)*.

Once the diagnosis of hematologic neoplasia was ruled out by biopsy of mediastinal adenopathy, it was decided to start treatment with rituximab. During the infusion, despite adequate premedication and infusion rate, the patient had a severe adverse reaction, so treatment with rituximab was suspended and led us to reconsider the indication. He continued with azathioprine treatment at a dose of 2 mg/kg/day. The patient showed favourable evolution with weight gain of 8 kg in 11 months and a significant clinical improvement. PET-CT scan showed a comparative decrease in size and metabolic activity of supra and infra diaphragmatic adenopathy; resolution of bilateral pulmonary opacities; and metabolic resolution of splenomegaly *(Fig. 2)*. Pulmonary function test results were normal.

At 18 months the treatment was suspended, and the patient remained clinically stable with stable pulmonary function test results 3 years after suspending the treatment and without significant changes on PET-CT scan.

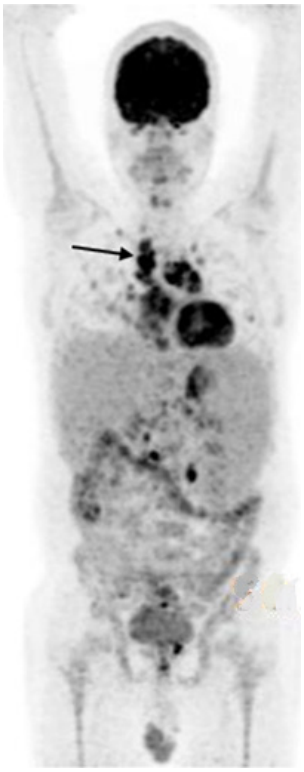


Figure 1. Baseline positron emission tomography-computed tomography scan: Supra- and infradiaphragmatic hypermetabolic adenopathy. At mediastinal level, the most relevant, at the upper right paratracheal-space (black arrow). Measures 39.8 mm. SUV 11.8.



Figure 2. Post-treatment positron emission tomography-computed tomography scan: No evidence of pathological concentration of radiotracer. Adenopathy at the upper right paratracheal-space (blue arrow). Measures 17.6 mm.

DISCUSSION

The treatment of patients with GLILD is currently a matter of study and discussion. There are numerous case reports, with various therapeutic schedules and some reviews on the subject, but there are still no publications on randomized controlled studies on a larger scale that objectively justify the approach. Among these reports, a tendency towards a higher frequency of GLILD relapses was observed in patients treated with corticosteroid monotherapy compared to rituximab treatment regimens according to qualitative endpoints[3]. The absence of quantitative data when measuring response to treatment is another point to highlight not only in case reports, but in some of the published series that are usually used as a reference when deciding on treatment[4]. Besides, it is noteworthy to mention the lack of information on long-term follow-up after discontinuation of treatment and the frequency of relapses according to the regimens used. In this context, the therapeutic decision is complex, and understanding the underlying pathophysiological mechanisms could bring us closer to the answer.

The analysis of the lymphocyte phenotype in peripheral blood and at the lungs in patients with CVID and GLILD would allow us to gain some insights into the pathophysiology of this condition. In peripheral blood, the reduction of $CD8^+$ T cells, regulatory T cells and post-switch memory B-cells, as well as the increase of IgM, $CD21^{low}$ and transitional B-cells, have been associated with the presence of ILD or its progression[5-7]. Coraglia et al. described an increase of follicular T helper (Tfh) cells in peripheral blood of patients with CVID and non-infectious complications[8]. Subsequently, other authors confirmed these findings and defined that the group of patients with non-infectious complications had a higher percentage of Tfh1 (non-B-cell helper) cells than patients without non-infectious complications, healthy subjects and a control group of sarcoidosis patients[5,6]. They demonstrated that increased serum Tfh1 was also observed at the lungs and in secondary lymphoid organs, which correlated directly with increased $CD21^{low}$ B-cells in these locations. The expansion of Tfh would in turn be associated with increased production of IFN-γ, with serum levels of this cytokine being responsible for the proliferation of $CD21^{low}$ B cells at both blood and lungs[5-7]. If we consider that T-cell regulation would have an overall impact on the development of the disease, the use of azathioprine could be a useful therapeutic option. The use of anti-CD20 alone has a limited effect on these T-cell populations, probably responsible for the relapses of the disease described in series with the use of rituximab as monotherapy[3,4]. The combination of rituximab with antimetabolite drugs is reported to have increased efficacy, but only limited data are available on the use of these medications as monotherapy to achieve long-term control of the disease, so it could be hypothesized that these drugs are responsible for the prolonged remission of the disease.

Since our patient did not receive rituximab due to an adverse reaction, it led us to reconsider the indication. We believe that it is necessary to review the rationale for the increasing use of anti-CD20 drugs in non-infectious complications in patients with CVID. Such use is based on expert recommendations and not on randomized, controlled studies with quantitative endpoints. It is important to keep in mind that CVID patients are a heterogeneous group, so no single treatment will be best for all of them. In addition, due to their rarity, it is difficult to group patients with similar GLILD and CVID phenotypes to properly investigate randomized treatments. Although evidence is still lacking to justify therapeutic decisions in GLILD, T-cell involvement could be the underlying cause of this complication and B-cell proliferation. Therefore, targeted T-cell treatments could represent a reasonable therapeutic option, as can be observed in our patient.

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