Successful treatment of interstitial pneumonia with autoimmune features using rituximab as salvage therapy

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Abstract
Interstitial pneumonia with autoimmune features is a complex and heterogeneous research classification without clear management and should be discussed on a case-by-case basis in a pluridisciplinary way. Rituximab could be used for severe lung involvement. The coronavirus crisis can hide other pathologies in such a way that a diagnosis can be overlooked.

KEYWORDS
autoimmunity, connective tissue disease, idiopathic interstitial pneumonia, interstitial lung disease, rituximab

1 | INTRODUCTION

Some patients with an idiopathic interstitial pneumonia (IIP) have autoimmune features but do not fulfill established criteria for a connective tissue disease (CTD). In 2015, the “European Respiratory Society (ERS) and American Thoracic Society (ATS) Task Force on Undifferentiated Forms of Connective tissue disease-associated interstitial lung disease” proposed the term “interstitial pneumonia with autoimmune features” (IPAF). The classification criteria for IPAF is a combination of three domains: clinical features, serologic features, and morphologic features. The physiopathology of the disease remains unclear, and there is no specific treatment so that corticosteroids and immunosuppressive agents are the mainstay of the treatment.

Interstitial lung disease (ILD) is associated with considerable morbidity and mortality. There can be a lack of therapeutic response in very severe lung involvement despite maximal conventional treatment, in such a way that rituximab (Rtx) may be an effective medical rescue therapy for ILD unresponsive to conventional immunosuppressive treatment.

We present a patient with IPAF treated successfully with rituximab used as salvage therapy.
started and since the patient needed oxygen supplementation, he was transferred to the intensive care unit (ICU) after a week of hospitalization. An escalation therapy by piperacillin/tazobactam and doxycycline was introduced with oxygen therapy of 8 L/min delivered via a mask but intubation was never required. Bronchoalveolar lavage showed a lot of macrophages and a low CD4/CD8 ratio with bacteriological and Pneumocystis Jiroveci research negative. Antinuclear antibodies (ANA) were positive with a 1:2640 titer and anti-RNP and anti-JO1 antibody identification without complement consumption. IPAF was established, and a treatment with corticosteroids 1 mg/kg/d of prednisone equivalent was started in the ICU. The patient was then transferred to the Internal Medicine Department for his management where mycophenolate mofetil (MMF) was added about 12 days after corticosteroids, increasing dosage over 15 days up to 2500 mg per day. Unfortunately, there was no improvement of his condition after 3 weeks with corticosteroids. His need of oxygen did not decrease so that supplemental oxygen with 8 L/min delivered via nasal prongs was required for an SpO$_2$ of 92% in a resting condition. He desaturated with exercises at SpO$_2$ of 80%. Pulmonary function tests were unrealizable at that time. We decided to start rituximab (Rtx) as salvage therapy with two doses of 1 g at an interval of 15 days. After a few days, his need of oxygen decreased and he was moved to a rehabilitation center for recovery 2 months after his admission with oxygen needs of 3 L/min delivered via nasal prongs. At a 4-month follow-up, he no longer needed oxygen and the thoracic computed tomography control showed significant improvement (Figure 2).

The patient’s informed consent for the treatment and for the description of this clinical case was obtained. Figure 3 shows a summary of his clinical history.

3 | DISCUSSION

Interstitial pneumonia with autoimmune features is not a diagnosis in itself, but a term used for patients with idiopathic interstitial pneumonia and features of autoimmunity who did not fall within the criteria of a connective tissue disease. In 2015, a multidisciplinary task force proposed classification criteria for IPAF. Those criteria are organized around features of three domains: a clinical domain consisting of specific extrathoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathology, or pulmonary physiologic features. According to Fischer et al, our patient had the criteria with a CT scan pattern of NSIP and OP, high titer of ANA with anti-RNP and anti-JO1 identification, and polyarticular morning joint stiffness over an hour.

The main differential diagnosis arises with antisynthetase syndrome (AS) and mixed connective tissue disease (MCTD). On the one hand, AS is an autoimmune condition characterized by the presence of anti-aminocetyl tRNA-synthetase autoantibodies associated with ILD, myositis, Raynaud’s phenomenon, and arthritis. Two classification criteria are available: Connors et al in 2010 and Solomon et al in 2011. The patient certainly satisfies Connors et al criteria (presence of anti-aminocetyl tRNA-synthetase with ILD and fever) but not Solomon et al which are the last criteria with the presence of anti-aminocetyl tRNA-synthetase and ILD as only major criteria but the absence of minor criteria (clinical arthritis, Raynaud’s phenomenon, and mechanic’s hands). Indeed, patient has anti-JO1 antibody identification but serum CPK was normal and as he had no myalgia, neither electromyography nor muscle biopsy has been performed. However, IPAF is point of uncertainties and controversies as it represents an overlap between idiopathic pulmonary fibrosis (IPF) and CTD-ILD. In particular, inclusion of myositis-specific antibodies (MSAs) in the IPAF criteria
can be confusing because these patients also satisfy criteria for an AS suggesting that MSAs are distinct IPAF phenotypes with clinical features and issues like patients with ILD due to an idiopathic inflammatory myopathy (IIM). As a result, Graham et al.\(^9\) proposed that MSAs should be removed from the IPAF criteria and patients managed as an IIM-ILD.

On the other hand, MCTD is a connective tissue disorder characterized by the presence of high titers of a distinct autoantibody to ribonucleoprotein (anti-U1-RNP antibody) and clinical features of systemic lupus erythematosus, systemic sclerosis, polymyositis, and rheumatoid arthritis.\(^10\) Nevertheless in this case, patient had anti-RNP in the absence of clinical features, hematologic abnormalities, or dysphagia.

There is no specific treatment as IPAF is a research consensus statement and not a well-defined entity. Management consists of global care with pulmonary rehabilitation, oxygen therapy if necessary, prevention of infection, and bone health assessment.\(^1\) Corticosteroids and immunosuppressive agents are usually used. For example, azathioprine and mycophenolate mofetil (MMF) are associated with improvement or stabilization of lung function.\(^1\) In this case, the patient received a combination of corticosteroids and MMF without improvement. He was considered as a patient with refractory ILD, and Rtx treatment was given as salvage therapy with an improved therapeutic response. A retrospective study indicates efficacy of Rtx in patients with AS and ILD. Indeed, this study demonstrated a reduction in ILD extent post-therapy.\(^6\) Doyle et al also showed that in ILD with AS, the principal indication for Rtx use was recurrent or progressive ILD due to failure of other agents resulting in stability or improvement in pulmonary function or severity of ILD on CT scan with a good tolerance of the treatment.\(^11\)

In our case, the presence of anti-JO1 antibodies may be a favorable prognosis to a good therapeutic response to Rtx as we can see in the AS.

In 2012, Keir et al showed the benefits of using Rtx as a life-saving therapeutic intervention in severe CTD-ILD with failure to conventional immunosuppression. In his study, patients improved pulmonary function with Rtx.\(^3\) In 2016, Lepri et al.\(^12\) demonstrated that Rtx may help to control the course of ILD in CTD producing a stabilization of lung involvement in systemic sclerosis and mixed connective tissue disorders.

According to Saunders et al.\(^13\), there are no approved therapies for CTD-ILD: Cyclophosphamide is the main therapy for patient with severe or progressive CTD-ILD but observational studies suggested that Rtx is an effective rescue therapy for refractory CTD-ILD.

Recently, Atienza-Mateo et al.\(^14\) demonstrated that Rtx was a good therapeutic option to preserve lung function in patients with IPAF.

### 4 | CONCLUSION

Interstitial pneumonia with autoimmune features is a research classification without specific treatment approach due to its heterogeneity. Management should be discussed on a case-by-case basis in a pluridisciplinary way. Further studies should be carried out to achieve an effective therapeutic approach. Rituximab could be considered in patients with severe lung involvement.
CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
AK: wrote the manuscript. YG and MC: were actively involved in the clinical care of the patient. All authors read and approved the final manuscript.

CONSENT STATEMENT
Published with written consent of the patient.

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