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CLINICAL NOTE

Quick response to rituximab in a patient with Ro52-Jo1 complex-associated antisynthetase syndrome debuting with rapidly progressive interstitial lung disease and diffuse alveolar haemorrhage

Rápida respuesta a rituximab en un paciente con síndrome antisintetasa asociado a anti-Ro52-Jo1 que debuta con enfermedad intersticial rápidamente progresiva y hemorragia alveolar difusa

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Abstract

Antisynthetase syndrome (AAS) is an inflammatory myopathy that may debut with interstitial lung disease (ILD). A few studies show cases in which patients with high concentrations of anti-Ro52 in patients with ILD might achieve a better response if treated with rituximab than other patients with ILD and Ro-52 whose levels are lower. We present a patient with lung involvement as the first and unique manifestation of AAS with anti-Jo and anti-Ro52-positive antibodies. The ILD was rapid and progressive and led him into the intensive care unit in a matter of days, despite several immunosuppressive treatments. As soon as the patient received this treatment, he experienced an improvement. We therefore suggest the prompt determination of anti-Ro52 antibody concentrations in this subgroup of patients, which would offer a therapeutic approach based first on rituximab over other immunosuppressive treatments.

Keywords: *Antisynthetase syndrome. anti Ro-52. anti Jo1. alveolar haemorrhage. Rituximab.*

Resumen

El síndrome antisintetasa (SA) es una miopatía inflamatoria que puede debutar en forma de enfermedad pulmonar intersticial (EPI). Algunos estudios muestran casos de pacientes con EPI secundaria a miopatía inflamatoria y positividad de anti-Ro52 a altas concentraciones que presentan mejor respuesta a rituximab que pacientes similares con positividad de anti-Ro52 a bajas concentraciones. Presentamos un paciente con enfermedad intersticial como primera y única manifestación de SA y con positividad para anti-Ro52 a concentraciones altas y anti-Jo1. La EPI fue rápida y progresiva, conduciéndole a ingreso en la unidad de cuidados intensivos e intubación orotraqueal a pesar de varios tratamientos inmunosupresores. Solo experimentó

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mejoría cuando se inició rituximab. Por ello, proponemos medir los títulos del anticuerpo contra Ro-52 en todos los pacientes con EPI secundaria a SA y positividad de anti-Ro52, y si se evidencian valores altos decidir rituximab como tratamiento de primera línea antes que otras terapias inmunosupresoras.

Palabras clave: *Síndrome antisintetasa. Anti-Ro-52. Anti-Jo1. Hemorragia alveolar. Rituximab.*

Introduction

Antisynthetase syndrome (ASS) is an autoimmune disease that may debut with any of the classic triad symptoms (interstitial lung disease [ILD], myositis, and arthritis), associated with aminoacyl tRNA-synthetase (anti-ARS) antibodies[1,2]. It is suggested that different ASS phenotypes might be associated with the appearance and severity of clinical manifestations. ILD plays a crucial role in morbidity and mortality.

Clinical observation

We report the case of a 53-year-old man presenting with fever, chest pain, cough, and dyspnoea for 1 week. He was an ex-smoker (20 years) and had no personal medical history. The patient worked in construction but indicated no exposure to environmental toxicants. He was admitted because of respiratory failure secondary to bilateral pulmonary opacities on chest X-ray. Bronchoscopy with bronchoalveolar lavage was undertaken, and several microbiological tests were performed, including a real-time reverse transcriptase-polymerase chain reaction test for SARS-CoV2 infection, which were all negative. High-resolution CT revealed bilateral alveolar infiltrates and diffuse ground-glass opacities with basal predominance (Figure 1A). The patient was started on broad-spectrum antibiotics, dexamethasone, and oxygen therapy, which was later switched to noninvasive ventilation because of worsening respiratory failure. Nine days after admission, the patient required endotracheal intubation in the intensive care unit. At this time, the results of the blood analysis were available, which showed positivity for anti-Jo1 and anti-Ro52 antibodies without other myositis-specific or -associated antibodies. Anti-Jo1 and anti-Ro52 antibodies were confirmed by qualitative immunoblotting. We also quantitatively determined the specific IgG antibodies directed against SS-A/Ro52 in serum using a two-step chemiluminescence assay (ZENIT RA SS-A/Ro52 kDa test, Menarini Diagnostics, Florence, Italy). The measurability range for the assay is 0.0-640 UA/ml; results were considered positive if > 10 UA/ml and negative if < 10 UA/ml. The patient was positive for SS-A/Ro52 and anti-Jo1, with a value of 544 UA/ml for SS-A/Ro52.

The patient was diagnosed with ASS and rapidly progressive interstitial lung disease (RP-ILD). He was treated with pulse intravenous methylprednisolone (1000 mg) for 3 days, followed by 1 mg/kg (80 mg/day) and tacrolimus (13 mg/day). Subsequently, he received immunoglobulins for 5 days; however, he experienced worsening with haemoptysis, anaemisation, and new diffuse alveolar consolidations (Figure 1B). A second bronchoscopy confirmed diffuse alveolar haemorrhage (DAH) secondary to ASS after discarding other possible causes such as infection. Treatment with plasmapheresis was started, with no improvement in the next few days. Finally, due to the high levels of anti-Ro52, we initiated treatment with 1 g of rituximab. The patient gradually improved and was extubated after 10 days. He received a second dose of rituximab after 2 weeks and continued on tacrolimus and prednisone when discharged 2 months after admission. He experienced a successful evolution with normalisation of pulmonary function tests and disappearance of the pulmonary infiltrates (Figure 1C and 1D). The patient returned to a normal life.

Discussion

The patient had a rapid initial presentation, which could be explained by the antibodies and their concentrations he had. It has been suggested that the anti-Ro52-anti-Jo1 (high concentrations) complex is a biomarker of a more acute form of ILD[4]. It might be rapidly progressive and is uncommon in patients who are anti-Jo1-positive[2]; however, association with anti-Ro52 and a phenotype without muscle involvement appear to be related to a poorer prognosis for ILD[3]. DAH is an exceptional complication of ASS and has a poor prognosis, with mortality ranging from 25 to 50%[5]. Acute alveolitis damages the alveolar-capillary membrane and might be related to pulmonary small-vessel involvement, causing pulmonary capillaritis and secondary DAH[5]. We discarded other causes of DAH in our patient, such as vasculitis, coagulopathy, other connective tissue diseases, thrombotic microangiopathies, infections, neoplasm, or drugs. A literature review using the terms ‘pulmonary capillaritis’, ‘diffuse alveolar

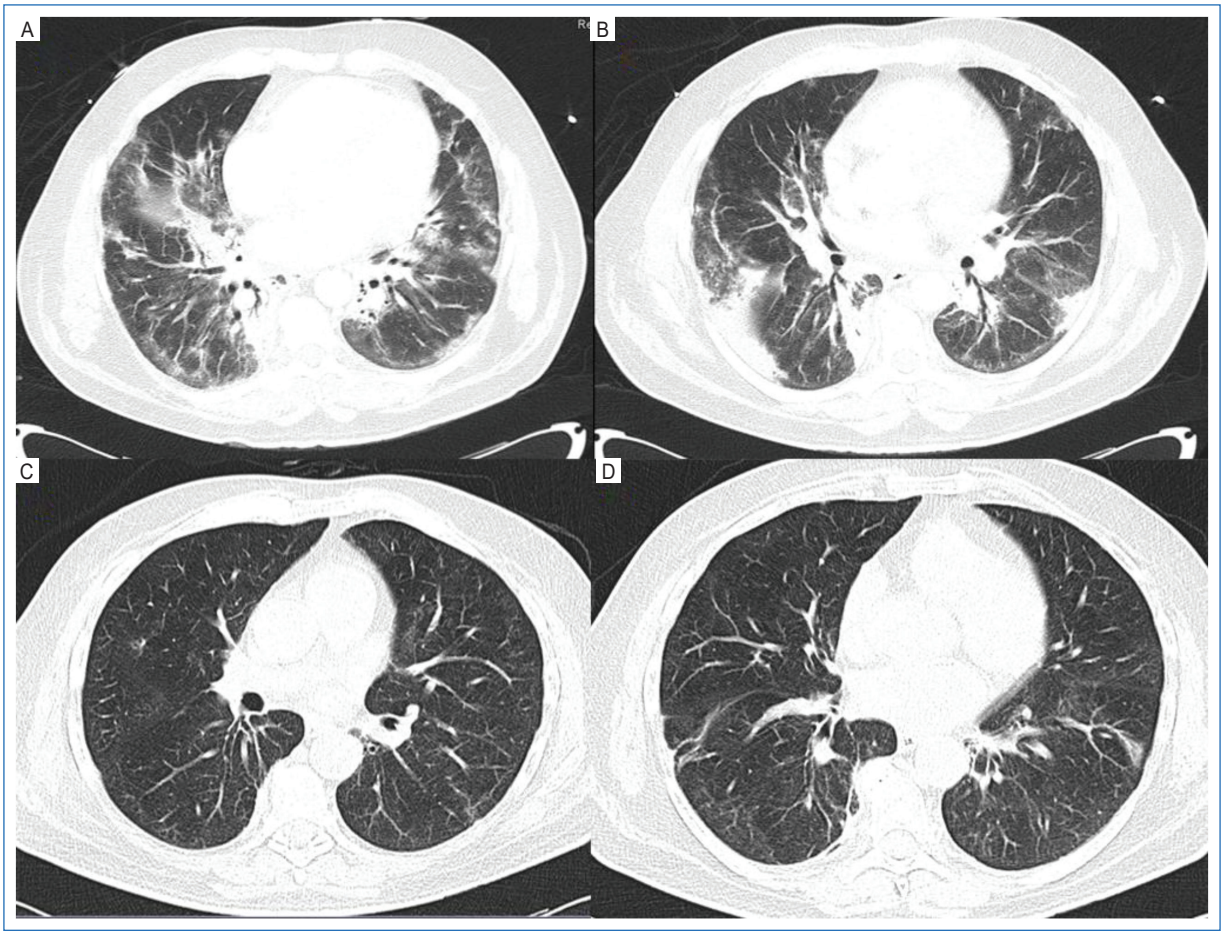

Figure 1. A: bilateral alveolar infiltrates and diffuse ground-glass opacities with basal predominance. **B:** new alveolar consolidations secondary to diffuse alveolar haemorrhage. **C** and **D:** resolution of the infiltrates after rituximab treatment and patient extubation.

haemorrhage', 'antisynthetase', 'synthetase', 'anti-jo1', 'anti-pl7', 'anti-pl12', 'anti-Ej', 'anti-Oj', 'anti-KS', 'anti-YRS/Ha', 'anti-Zo', and 'anti-Ro52' highlighted only six reported cases of DAH and ASS with the following antibodies: 2 anti-Pl7, 1 anti-Pl12+anti-Ro52, 1 anti-Pl12, 1 anti-Jo1, and 1 not specified[5-8].

We initially elected to start tacrolimus with glucocorticoids based on the extensive experience of this drug in idiopathic inflammatory myopathies with RP-ILD-like anti-MDA5 syndrome[9]. Cyclophosphamide was not elected as it could lead to serious infectious complications in a patient with a high risk of infections (a severe flare of an autoimmune disease in conjunction with intense immunosuppressive treatment in a patient admitted in the intensive care unit). However, we believe tacrolimus was ineffective due to the rapid emergence of DAH. We then switched to rituximab, as a better response with this treatment has been described in patients with Jo1 antibody-associated ASS and high anti-Ro52 antibody concentrations than with conventional immunosuppressive therapy[4]. Our patient experienced a very rapid and good response, previously not reached with glucocorticoids, immunoglobulins, or tacrolimus. Our case highlights that patients with Ro52-Jo1 complex-associated ASS may debut with RP-ILD, which may lead to severe complications, including DAH. A fast and efficient response might be achieved if there are high anti-Ro52 antibody concentrations. We therefore suggest the prompt determination of anti-Ro52 antibody concentrations in these subgroups of patients, which would offer a therapeutic approach based on rituximab over other immunosuppressive treatments.

Funding

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patient mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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