



Antisynthetase Syndrome and Rheumatoid Arthritis: A Rare Overlapping Disease

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Abstract

The association between Antisynthetase Syndrome (ASS) and rheumatoid arthritis is extremely rare. In this case report, we are describing a 16 years long standing history of seropositive RA before its uncommon association to an ASS. A 55-year-old female patient presented at the first visit with symmetric polyarthritis and active synovitis affecting both hands and ankles. Laboratory investigations showed positive rheumatoid factors, positive anti-CCP antibodies and negative ANA. The X-rays were consistent with typical erosive in hands. Thus, the patient fulfilled the ACR 1987 criteria of RA in 2000 at the age of 37. Methotrexate was firstly prescribed. However, it was ineffective after 4 years. Then, the patient did well with Leflunomide until January 2017, when she developed exertional dyspnea. High-resolution CT of the lung revealed Nonspecific Interstitial Pneumonia (NSIP). Autoantibodies against extractable nuclear antigens were screened and showed positive results for anti-Jo1 autoantibodies. She was diagnosed with ASS complicating the course of RA.

Keywords: Antisynthetase syndrome; Rheumatoid arthritis; Overlap syndrome; Nonspecific interstitial pneumonia

Key Points

- Antisynthetase Syndrome should be considered as a clinical manifestation of overlap syndromes, particularly in active RA patients with pulmonary signs and anti-Jo-1 antibody.
- An early diagnosis of antisynthetase syndrome in an overlap syndrome is important, as treatment may need adjustment.

Introduction

Antisynthetase Syndrome (ASS) is a systemic autoimmune connective tissue disease, characterized by the association of interstitial lung disease, inflammatory myopathy, Raynaud phenomenon, and/or mechanic's hands with the presence of anti-aminoacyl-transfer RNA synthetase antibodies [1].

Approximately 5% to 8% of cases of Antisynthetase Syndrome (ASS) manifest as overlap syndromes with another connective tissue disease such as systemic lupus erythematosus, systemic sclerosis or Sjögren's syndrome [1]. However, the co-existence of ASS and Rheumatoid Arthritis (RA) has been rarely described [2-5]. The particularity of ASS when it is associated to other diseases is the presence of the antibody anti-Jo-1, while other antisynthetase specificities (e.g., anti-PL-7, PL-12, EJ, KS, OJ, YRS, and Zo) are less frequently identified [6].

Here, we describe the case of a female RA patient who developed ASS, and provide a review of the pertinent literature.

Case Presentation

A 55-year-old female patient presented in September 2000, with symptoms of morning stiffness, symmetrical polyarthritis, joint swelling and tenderness affecting both hands and ankles. No symptoms or signs suggestive of extra-articular features were detected. Laboratory investigations at diagnosis showed elevated levels of inflammatory markers such as C-Reactive Protein (CRP) and Elevated Erythrocyte Sedimentation Rate (ESR). Her serum was positive for Rheumatoid Factor (RF) and anti-Citrullinated Protein Antibodies (anti-CCP) (160 IU/ml and 120 IU/ml respectively). She had negative fluorescent Antinuclear Antibodies (ANA). The plain X-rays of both hands showed typical erosive changes affecting the carpal bones with narrowed radio-carpal joints on both

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Figure 1: Wrist and hand X-rays showing typical erosive changes affecting the carpal bones.

sides, subluxation of the fifth interphalangeal joint consistent with the diagnosis of RA (Figure 1). Thus, the patient fulfilled the ACR 1987 criteria of RA at the age of 37 years-old. The patient did not show much improvement on Methotrexate (MTX) 10 mg/week/po, folic acid supplements and a low dose of steroids (prednisolone 5 mg/d/po). MTX had been withdrawn due to digestive disorders on January 2004 and switched to Leflunomide. Then, the patient showed marked improvement and she remained in remission with DAS 28 (Disease Activity Score 28 points) \leq 2.6. An episode of erythema nodosum was noted in 2007, leflunomide was exonerated and resumed. Other causes were eliminated by appropriate explorations.

In September 2016, the patient was admitted to our hospital with fatigue, alteration of the general condition, intense myalgia, and proximal muscle weakness affecting both thigh muscles. Neurological examination showed reduced muscle power in shoulder and pelvic girdles rated at 3- and 2+. Shortly after, the patient started to develop dry cough and exertional dyspnea. She had no Raynaud's phenomenon and no signs of gastroesophageal reflux. Eruptions including Gottron's papule, heliotrope rash, or mechanic's hand were not detected.

Laboratory examinations showed high CRP and ESR levels (20.9 mg/L and 58 mm/h respectively). Serum lactate dehydrogenase was 4.5 times above the normal (2140 U/L), serum creatine kinase was 20 times above the normal (3530 IU/L), serum aspartate transaminase was 9 times above the normal (418 U/L) and serum alanine transaminase was seven times above the normal (311 U/L). The autoantibody profiles showed positive anti-Jo-1 and negative ANCA and cryoglobulinemia. Chest ray was not relevant. High-Resolution Computed Tomography (HRCT) of the chest revealed Nonspecific Interstitial Pneumonia (NSIP) (Figure 2). Respiratory assessment showed a restrictive syndrome and a DLCO at 58% of the predictive value.

Electromyography findings revealed typical myogenic pattern consistent with inflammatory myopathy. Based on these findings, she was diagnosed with antisynthetase syndrome overlapping with RA.

The patient received 1 mg/kg of methylprednisolone and Leflunomide was maintained. The treatment was highly successful: proximal muscle weakness and exertional dyspnea improved; besides, muscle enzyme levels were normalized. However, after 6 months of treatment, at the dose of 10 mg of steroids her respiratory symptoms as well as restrictive syndrome were aggravated. She was putted on Azathioprine for three months then stopped due to digestive intolerance. A treatment based on cyclophosphamide was then

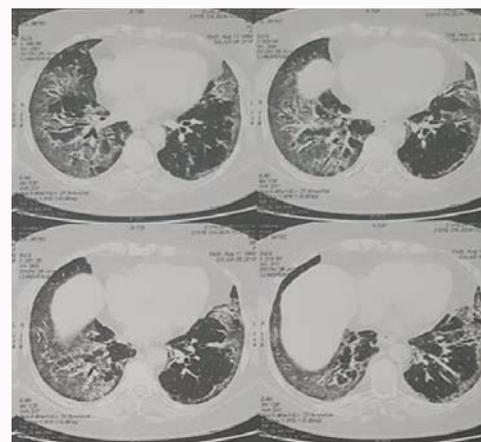


Figure 2: Chest scan revealing Non-Specific Interstitial Pneumonia (NSIP).

prescribed. She received six intravenous injections with a marked improvement. Currently, after four months from the end of the intravenous injections, she is being treated with steroids at a dosage of 10 mg and MTX injections as Leflunomide was stopped because of hypertension. Her last muscular testing found normal power and last blood samples showed normal levels of muscular enzymes. A respiratory assessment is scheduled for the next follow-up.

Discussion

In this report, we described a case with longstanding history of seropositive RA and rare association with ASS, which was previously reported in only few case reports.

ASS is a systemic autoimmune connective tissue disease, characterized by the association of Interstitial Lung Disease (ILD), inflammatory myopathy, Raynaud phenomenon, and/or mechanic's hands with the presence of Anti-aminoacyl-transfer RNA Synthetase (anti-ARS) antibodies [7].

The association of Polymyositis (PM)/Dermatomyositis (DM) with RA is well known from longtime. About 3% to 20% of patients with PM/DM have overlapping characteristics of RA [8]. However, the association between ASS and RA is extremely rare and the current available data is still limited and mostly came from case reports [2-5]. Indeed, this association was firstly described by Meyer et al. [9].

ASS was diagnosed 16 years after RA. In a study including 40 cases of anti-CCP negative polyarthritis revealing ASS, the mean delay between the onset of polyarthritis and ASS diagnosis was 27 months, with late occurring for pulmonary and muscular symptoms [10]. From a clinical point of view, symptoms of ASS in our patient consisted on myositis and lung disease. Manifestations such as arthritis, myositis, and ILD were observed in up to 90% of cases, whereas features such as Raynaud's Phenomenon (RP), Fever and Mechanic's Hands (MH) were less frequently reported (30%, 32% and 25% respectively) [10]. Joint manifestations were present in 21% to 32% of patients with ASS. Subluxation arthropathy has been described in 19% of anti-Jo1-ASS patients, whereas joint damages were less common, ranging from 0% to 8% [11]. The articular manifestation in our patient was similar to those previously described in the literature.

Anti-Jo-1 antibodies were reported to be positive in about 25% of patients with PM/DM [12]. Anti-ARS (Autoantibodies against aminoacyl-tRNA synthetases) antibodies recognize ARSs in many

cells, including myocytes; six major anti-ARS antibodies: Histidyl-(Jo-1), alanyl-(PL-12), threonyl-(PL-7), isoleucyl-(OJ), glycy-(EJ), and asparaginy-tRNA synthetase (KS) have been reported to date [12]. However, the clear pathophysiological roles of these antigens have not yet been clarified. Nevertheless, a molecular mimicry theory has been proposed involving an interaction between virus and antisynthetase antibodies [13].

In our case, ANA was negative. Recently, Imed et al. showed that positive ANA is positively associated with anti-Ro, anti-La and anti-Jo1 autoantibodies [14]. Thus, screening for auto-antibodies against other anti-ENAs (Autoantibodies against extractable nuclear antigens) when ANA is positive seems mandatory in RA patients [14]. However, negative ANA do not indicate negative autoantibodies seen in ASS and should not exclude this diagnosis as in our case presentation [15]. Anti CCP presence seems discriminant for the diagnosis of ASS associated to RA. However, these antibodies seem to be present in some cases of myositis [10]. When erosions were also present, the nosologic diagnosis between ASS and RA could be difficult [10]. Moreover, anti CCP-positive ASS patients displayed extra-rheumatic manifestations similar to anti CCP-negative ASS patients even with ILD and were at high risk of developing erosive arthritis refractory to DMARDs (Disease-Modifying Antirheumatic Drugs). Our patient was treated with high dose of corticosteroids and cyclophosphamide pulses for the pulmonary involvement associated with leflunomide as previously prescribed for its RA. The study of Ochi et al. [16] described PM as a complication caused by leflunomide rather than an overlap syndrome. However, in this study, when PM developed, ANA and Anti-Jo-1 were not detected [16]. In our case, it seems unlikely that the RA medication induced the ASS as leflunomide was prescribed for many years prior without adverse effects. Furthermore, anti-Jo-1 antibodies were present in our case. Similarly, five case reports suggested an unusual association between the onset of PM/DM with anti-Jo-1 antibody and anti-TNF therapy for RA [2-5]. This may be explained by adverse immunologic events including the development of ANA and anti-DNA antibodies as part of lupus-like disease.

Unlike anti-TNF drugs, anti-CD20 may be effective and well tolerated in patients with ASS associated to RA. This is an interesting alternative which did not exacerbate extra-articular involvements [17]. Indeed, this biologic was proposed as a “rescue therapy in ASS patients suffering from progressive and refractory ILD [17]. As in the study of Keir et al. [17] where patients with ASS and severe ILD showed significant improvement in pulmonary symptoms and lung function [17].

Our case corresponds to a real overlap syndrome between RA and ASS, fulfilling both classification criteria. This association highlights the usefulness of lung evaluation in case of recent onset arthritis. Therapeutic implications for this coexistence are not consensual since this situation is uncommon and need clarifications.

Conclusion

In conclusion, ASS is a rare systemic disease, which may complicate the course of RA. This case demonstrates that overlap syndromes have variable presentations, and that ASS should be considered as a clinical manifestation of overlap syndromes, particularly in active RA patients presenting with pulmonary manifestations associated with ANA and anti-Jo-1 antibody. This rare under recognized entity should be more studied in order to examine the prevalence of anti-Jo1

antibodies in RA patients as well as its clinical relevance.

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