

Antisynthetase syndrome with rare EJ-1 antibodies with antiphospholipid syndrome

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Abstract

We describe the first case of antisynthetase syndrome (ASS) with antibodies to anti-glycyl tRNA synthetase (EJ-1) with antiphospholipid syndrome (APLS). A 66-year-old man presented with progressive dyspnoea, fever, dry cough and proximal muscle weakness over several months on a background of cryptogenic organizing pneumonia. Examination revealed bibasal fine chest crackles, proximal muscle weakness of the upper and lower limbs, digital skin thickening and facial telangiectasias. Creatine kinase was elevated and autoimmune screening was positive for anti-EJ-1, anti-beta-2-glycoprotein, anti-Ro and anti-La antibodies. Computed tomography of the chest revealed a usual interstitial pneumonia pattern and a ventilation–perfusion scan demonstrated scintigraphic evidence of bilateral pulmonary emboli. A diagnosis of ASS and APLS was made. Immunosuppressive therapy including pulsed methylprednisolone, rituximab and mycophenolate was commenced with improvement in symptoms. This case highlights the importance of evaluation for ASS in idiopathic interstitial pneumonia, and APLS in ASS patients.

KEYWORDS

antiphospholipid syndrome, antisynthetase syndrome, EJ-1 antibody, interstitial lung disease, myositis

INTRODUCTION

Antisynthetase syndrome (ASS) is a rare autoimmune condition involving antibodies to aminoacyl transfer RNA synthetase. This classically manifests as a triad of myositis, arthritis and interstitial lung disease (ILD), although this occurs in less than 20% of cases.^{1,2} ASS often presents as isolated ILD making the diagnosis challenging, leading to delays in diagnosis and thereby impacting treatment and prognosis.³ Treatment options include glucocorticoids, steroid-sparing agents such as mycophenolate and azathioprine, and rituximab in refractory cases.⁴ The association with pulmonary embolism has been limited to case studies, and there is limited literature detailing the association with antiphospholipid syndrome (APLS).^{5–8} To our knowledge, we present the first case of anti-EJ-1 ASS with APLS.

CASE REPORT

A 66-year-old Caucasian male re-presented to hospital with progressive dyspnoea (Medical Research Council dyspnoea score 3), fever, dry cough and proximal muscle weakness over several months. This was on a background of cryptogenic organizing pneumonia (COP).

The diagnosis of COP was established 5 years earlier on video-assisted thoracoscopic surgery lung biopsy and confirmed in an ILD multidisciplinary meeting. Auto-antibodies at the time were all negative, including anti-nuclear antibody (ANA), extractable nuclear antigens, anti-double-stranded DNA and antineutrophil cytoplasmic antibodies (ANCA). In the absence of arthritis and myalgia, screening for myositis-specific antibodies was not performed. Chest high-resolution computed tomography (HRCT) showed patchy ground-glass opacities in a bibasal distribution with

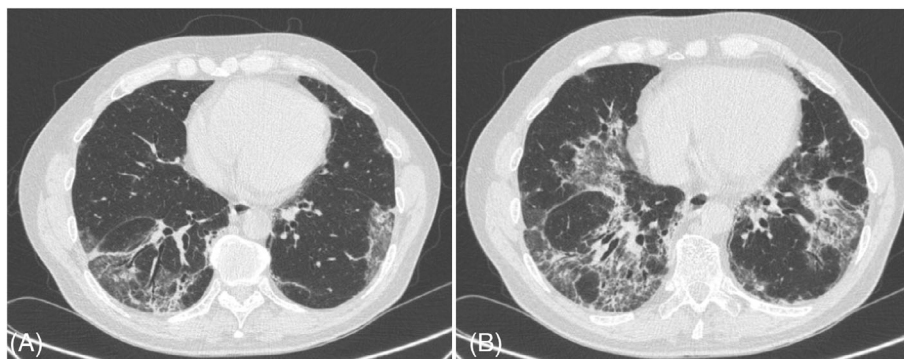


FIGURE 1 At baseline, (A) axial chest high-resolution computed tomography (HRCT) of the middle lung zones demonstrating reticulations and (B) axial chest HRCT of the lower lung zones demonstrating patchy ground-glass opacities, intralobular septal thickening and traction bronchiectasis

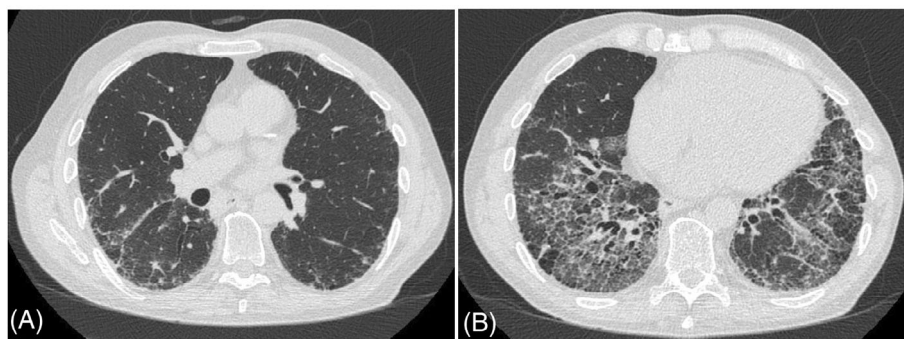


FIGURE 2 Upon presentation to hospital with dyspnoea 5 years later, (A) axial chest high-resolution computed tomography (HRCT) of the middle lung zones demonstrating reticulations and (B) axial chest HRCT of the lower lung zones demonstrating honeycombing and traction bronchiectasis in keeping with a usual interstitial pneumonia pattern

intralobular septal thickening and traction bronchiectasis (Figure 1). Initial respiratory function testing demonstrated a restrictive ventilatory deficit with a forced vital capacity (FVC) of 2.71 L (61%) and a diffusing capacity for carbon monoxide (DLCO) of 70% predicted. Initial therapy included high-dose prednisolone with significant symptomatic improvement and normalization of FVC and DLCO. Regular monitoring was performed clinically and with serial respiratory function tests. He relapsed off treatment 4 years later, requiring prednisolone and azathioprine as a steroid-sparing agent with subsequent improvement in symptoms, FVC and DLCO.

Other past medical history was significant for ischaemic heart disease and cardiomyopathy with three coronary stents, use of dual antiplatelet therapy, coeliac disease, obstructive sleep apnoea and dermatitis herpetiformis (treated with dapsone 100 mg daily).

On admission, he required oxygen supplementation at 2 L/min saturating at 93% and was haemodynamically stable. Pulmonary findings on physical examination demonstrated fine bibasal crackles with reduced chest expansion. Extrapulmonary findings included proximal weakness of both upper and lower limbs, skin tightening and thickening of the fingers, nailfold capillary loop dilations and facial telangiectasias.

Full blood examination showed chronic normocytic anaemia with a haemoglobin of 100 g/L. His renal function and liver function parameters were unremarkable. Creatine kinase (CK) level was elevated at 756 IU/L. C-reactive protein was elevated at 48.0 mg/L and erythrocyte sedimentation rate elevated at 63 mm/h. Coronavirus polymerase chain reaction was negative twice. Multiple blood cultures, urine culture, cytomegalovirus, Epstein–Barr virus, HIV and hepatitis serologies were negative.

Rheumatological workup revealed positive ANAs with a titre of 640. Anti-dsDNA, anti-topoisomerase I, anti-Scl-70, ANCA, anti-Smith and anti-U1RNP antibodies were negative. Antibodies were positive for anti-Ro, anti-La and myositis-specific anti-EJ-1.

Chest HRCT revealed bibasal predominant reticular thickening with subpleural involvement, evidence of honeycombing and traction bronchiectasis in keeping with a usual interstitial pneumonia (UIP) picture, in addition to an area of ground-glass opacity in the right upper lobe (Figure 2). Ventilation and perfusion scan demonstrated scintigraphic evidence of bilateral pulmonary emboli and antiphospholipid (APLS) screening was strongly positive for beta-2 glycoprotein IgG antibodies (>100 units/ml), prompting commencement of therapeutic enoxaparin and subsequent warfarin. Transthoracic echocardiogram revealed evidence of known

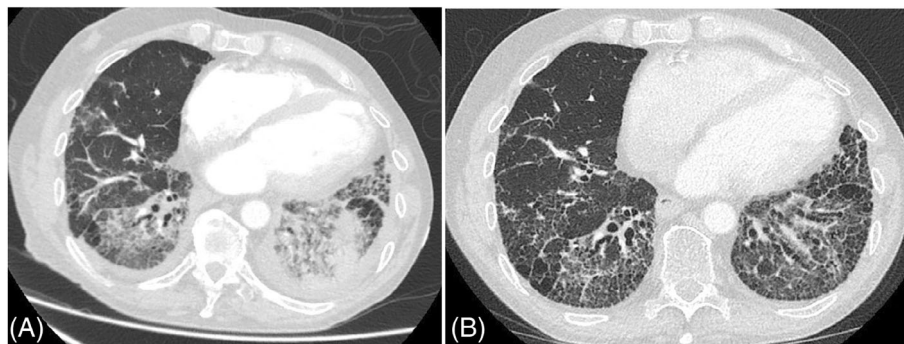


FIGURE 3 (A) Axial chest high-resolution computed tomography (HRCT) of the lower lung zones showing multi-focal consolidation with surrounding ground glass on a background of usual interstitial pneumonia changes upon presenting to hospital 3 months post diagnosis of antisynthetase syndrome and (B) subsequent axial chest HRCT of lower lung zones demonstrating interval resolution of consolidation and ground-glass changes, after the treatment of multi-lobar pneumonia

ischaemic left ventricular dysfunction, without pulmonary hypertension (PH).

Given the raised inflammatory markers, presence of anti-EJ-1 and clinical features of ASS, as well as failure to improve with antibiotics, a consensus diagnosis of ASS was reached via ILD multidisciplinary meeting and subsequent management involved intravenous (IV) methylprednisolone 1 g over 3 days followed by weaning prednisolone (from 50 mg) and commencement of mycophenolate mofetil. Due to the severity of respiratory symptoms and ongoing fevers, IV rituximab induction therapy was commenced. Dapsone was continued for *Pneumocystis jirovecii* pneumonia prophylaxis.

Three months following treatment, CK level and inflammatory markers had normalized and he was able to walk more than a kilometre (MRC dyspnoea score 1). However, he subsequently developed severe multi-lobar pneumonia (Figure 3), requiring a prolonged course of antibiotics and high-flow oxygen support which was subsequently weaned over 2 weeks. He experienced significant deconditioning with respiratory muscle weakness and required inpatient rehabilitation. He is currently on maintenance prednisolone of 10 mg daily, mycophenolate mofetil and supplemental oxygen on exertion. Repeat respiratory function tests demonstrated an FVC of 3.00 L (71% predicted) and a DLCO of 35% predicted. HRCT demonstrated interval improvement of consolidation and ground-glass changes (Figure 3). Repeat anti-beta 2 glycoprotein levels were normal post-rituximab therapy.

DISCUSSION

The prevalence of ASS is largely unknown, although the annual incidence of idiopathic inflammatory myopathies (IIMs) is 2–12 cases per one million adults, including local Australian data.^{4,9–11} The clinical presentation can be variable, with many patients presenting with isolated ILD in the absence of fever, myositis, Raynaud's phenomenon, inflammatory polyarthritis or the skin changes of mechanic's hands.⁴ In an international retrospective study of anti-Jo-1 ASS, 44 patients

(19.5%) had the clinical triad of arthritis, myositis and ILD on diagnosis, with only 50% of patients having developed the clinical triad at the end of follow-up.² Hence, repeating serological and clinical evaluation should be performed in cases of idiopathic interstitial pneumonia (IIP), as features of IIMs or other connective tissue diseases can appear later in the disease course, as was in our case. Furthermore, early evaluation with autoimmune screening including myositis-specific antibodies can potentially reduce the need for lung biopsy.³

ASS is considered a distinct clinical entity of IIM. Until recently, there have existed two main classification criteria by Connors et al. and Solomon et al., which require the presence of antibodies to aminoacyl transfer RNA synthetase and the specific clinical features.^{12,13} Myositis antibodies are often divided into Jo-1 and non-Jo-1 antibodies (anti-EJ-1, anti-PL-12, anti-PI-7, anti-OJ, anti-KS, anti-YRS/Ha, anti-SC, anti-Zo, anti-JS), with non-Jo-1 patients having worse outcomes and reduced survival.^{3,14} Antibody levels can fluctuate based on disease severity and not all laboratories test for all antibodies associated with ASS, thereby adding to the challenges of diagnosis.¹⁵ The most common radiological findings on chest computed tomography are non-specific interstitial pneumonia (NSIP) and COP, although UIP patterns are not infrequent.^{3,15} Histological specimens are often not utilized in diagnosis, but histopathological findings include diffuse alveolar damage, UIP and NSIP.

The mainstay of treatment is with glucocorticoids, with no randomized controlled trials to guide dosing and treatment. Additional steroid-sparing immunosuppressants including azathioprine and mycophenolate mofetil are often used, as recurrence of disease is common amongst steroid monotherapy and those with anti-EJ-1 antibodies.^{3,16} Rituximab has been demonstrated to be effective in refractory disease, with improvement or stabilization of lung parameters including FVC, DLCO and radiographic scoring, but treatment with rituximab should be carefully considered due to increased infection risk.^{17–19} In our case, despite a significant improvement in MRC dyspnoea score, DLCO did not improve which was likely reflective of concurrent pulmonary emboli and recent severe pneumonia.

Screening for PH is important amongst ASS patients, due to the association with increased morbidity and mortality, especially for non-Jo-1 positive patients.^{4,14,15,20} The importance of evaluation for PH in persisting dyspnoea and reduced exercise tolerance must be emphasized as targeted PH treatment may be of benefit.^{21,22} This was relevant in our case, due to the presence of multiple comorbidities that impacted his exercise capacity.

The association between ASS and APLS is limited to case studies,^{5–8} and to our knowledge APLS has yet to be described in association with anti-EJ-1 ASS. However, it should be noted that APLS has been described in patients with coeliac disease, and antiphospholipid titres in coeliac patients are significantly higher than control populations.^{23,24} Although repeat testing for APLS antibodies in our case was negative, treatment with rituximab has been demonstrated to normalize APLS antibody titres and there is evidence to suggest correlation with clinical improvement.^{25–27} Pulmonary embolism or APLS should therefore be considered amongst ASS patients given it can be treated. This was especially important in our case, as our patient already had poor prognostic factors due to EJ-1 antibody positivity and cardiac comorbidities.

ASS can be a challenging diagnosis due to its variability in clinical presentation and onset of clinical features. Our case highlights the importance of comprehensive serological and clinical evaluation for connective tissue diseases such as ASS and IIM, including serial assessments, in patients with IIP or unclassifiable ILDs. Furthermore, we described the first case of anti-EJ-1 ASS with APLS and raise awareness of the importance of diagnostic consideration of concurrent thromboembolic disease and APLS.

AUTHOR CONTRIBUTION

All authors were involved in the preparation of the manuscript.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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