CASE REPORT

Antisynthetase syndrome (ASS) presenting as acute respiratory distress syndrome (ARDS) in a patient without myositis features

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SUMMARY

A woman aged 61 years presented to the emergency room with a 1-week history of dyspnoea on exertion and dry cough. X-ray of the chest showed diffuse interstitial opacities and was started on antibiotics and furosemide, and despite these measures, patient's respiratory status worsened, prompting endotracheal intubation. CT of the chest showed diffuse bilateral ground glass opacities and underwent bronchoscope with trans-bronchial biopsy that showed chronic bronchitis. Pt was empirically started on intravenous steroids due to concerns for interstitial lung disease (ILD). Autoimmune work up was sent and underwent video-assisted thoracoscopic surgery-guided biopsy of the lung that showed non-specific interstitial pattern with fibrosis. The patient was diagnosed as having antisynthetase syndrome with pulmonary involvement (ILD) as the cause of her acute respiratory failure. Azathioprine was started as steroid-sparing agent and was weaned off the ventilator to a tracheostomy collar and discharged to long-term rehabilitation centre.

BACKGROUND

Antisynthetase syndrome (ASS) is a rare autoimmune disorder, first described in patients with polymyositis and dermatomyositis in 1990.¹ It is characterised by the presence of autoantibody against aminoacyl-transfer RNA synthetase, named antisynthetase antibody, and of which anti-Jo-1 antibody is the most common, predominantly found in 15–30% of patients with polymyositis and 60–70% of those with interstitial lung disease (ILD).^{1–2} ASS patients present with various clinical manifestations, including myositis, arthralgia or arthritis, ILD, Raynaud's phenomenon and mechanic hands. ILD is very frequent in ASS and reported in 60–70% of cases and drives the prognosis. Although ASS is included in the spectrum of inflammatory myopathies, myositis may be absent or delayed after lung involvement.^{1–4} Here, we report a first case of a woman aged 61 years who presented with acute respiratory distress syndrome (ARDS) and was subsequently diagnosed with ASS without any myositis features.

CASE PRESENTATION

A woman aged 61 years with a medical history of hypertension, heart burn, paroxysmal atrial fibrillation and diastolic heart failure presented to the emergency room (ER) with a 1-week history of shortness of breath on exertion and dry cough in December

2015. Pt was on aspirin, omeprazole and amlodipine at home and denied any fever, chills, chest pain, leg swelling, palpitations, joint swellings, muscle weakness, skin rash or any sick contacts. The patient has normal X-ray of the chest 2 weeks prior to admission (figure 1). Family history was significant for ILD in daughter per the patient, but we were not able to verify the specific type. The patient denied any history of smoking or any other drug use.

The patient was placed on oxygen as she was hypoxic on room air in the ER. Initial abnormal laboratory findings included elevated white cell count (WCC) of 13 330 with no left shift, mild normocytic anaemia with a haemoglobin level of 10.0 g/dL, elevated creatinine of 1.6 mg/dL and initial X-ray of the chest showed diffuse interstitial opacities (figure 2). Pt was admitted to the cardiology service for possible acute heart failure exacerbation and pneumonia.

She was started on antibiotics and furosemide, and despite these measures, patient's respiratory status worsened, prompting transfer to the intensive care unit (ICU) and subsequent endotracheal intubation. X-ray of the chest showed worsening infiltrates bilaterally with WCC elevated to 19 000 and the patient became febrile. Antibiotics were broadened after obtaining cultures and CT scan of the chest without contrast was ordered for further evaluation of the worsening infiltrates (figure 3). CT scan showed diffuse bilateral ground glass

Figure 1 X-ray of the chest showing normal lungs few weeks prior.

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Figure 2 X-ray of the chest showing bilateral interstitial opacities in the lung on admission.

Figure 3 CT scan of the chest showing bilateral ground glass opacities on admission.

opacities in the right middle and bilateral lower lobes. She underwent bronchoscopy with bronchoalveolar lavage (BAL) and trans-bronchial biopsy from the right lower lobe. Diffuse alveolar haemorrhage was ruled out based on BAL and all the cultures from the blood, urine and lung tissue were negative. Trans-bronchial biopsy from the lung showed chronic bronchitis.

The patient continued to require ventilator support, despite the broad-spectrum antibiotics and negative cultures and underwent tracheostomy. Trans-thoracic echocardiogram (ECHO) was obtained that showed normal ejection fraction with stage 1 diastolic dysfunction. A repeat CT scan of the chest without contrast was obtained to evaluate the previous opacities and showed worsening ground glass opacities in the lower lobes bilaterally with reticulation. Pt was empirically started on intravenous methylprednisolone (2 mg/kg) due to concerns for ILD, and rheumatology and thoracic surgery services were consulted.

INVESTIGATIONS

Autoimmune work up was sent and the patient underwent video-assisted thoracoscopic surgery -guided biopsy of the right lung. Autoimmune labs were remarkable for normal creatinine phosphokinase, positive anti-JO-1 and RO-52 antibodies (table 1) and lung biopsy showed non-specific interstitial pattern (NSIP) with fibrosis (figure 4).

DIFFERENTIAL DIAGNOSIS

At this time, differential diagnosis we had for this patient was:

- Idiopathic non-specific interstitial pneumonia (NSIP).

Table 1 Antibody profile in the patient

Antibodies	Result
Anti-JO-1	Positive
RO-52 Ab	Positive
RNP Ab	Positive
SS-A (Ro) Ab	Positive
CCP antibody	Positive
CRP	Elevated
ANA	Positive
CPK	Normal

Figure 4 Lung biopsy showing non-specific interstitial pneumonia pattern with fibrosis.

- NSIP due to underlying connective tissue disease.
- Acute interstitial pneumonia.
- Drug-induced pneumonitis.
- Organising pneumonia.

TREATMENT

The patient was diagnosed as having ASS with pulmonary involvement (ILD) as the cause of her acute respiratory failure. Azathioprine was started as steroid-sparing agent and gradual steroid taper was performed.

OUTCOME AND FOLLOW-UP

The patient was weaned off the ventilator and transferred to the regular medicine floor on tracheostomy collar. She was subsequently discharged to long-term rehabilitation centre as she was severely deconditioned from her prolonged ICU stay and long course of steroids.

DISCUSSION

ASS is a rare autoimmune disorder characterised by the presence of myositis-specific autoantibodies against aminoacyl-tRNA synthetase (ARS), named antisynthetase antibody, and of which anti-Jo-1 antibody is the most common.^{1–4} These antibodies are seen specifically and exclusively in idiopathic inflammatory myopathies—polymyositis and dermatomyositis—and are known as myositis-specific antibodies (MSA).¹

MSA are directed against cytoplasmic or nuclear components and the best known MSA autoantibodies are: anti-ARS autoantibody, anti-Mi-2 autoantibody and antisignal recognition particle autoantibody.^{1–3} Anti-ARS autoantibodies are also known as

Table 2 Case reports of antisynthetase syndrome presenting as acute respiratory distress syndrome without myositis

Number of cases	Type of study	Reference
3	Case series	Clawson and Oddis ⁵
1	Case report	Monia <i>et al</i> ⁶
1	Case report	Polosa <i>et al</i> ⁷
1	Case report	Guglielmi <i>et al</i> ⁸
1	Case report	Fagedet <i>et al</i> ⁹
1	Case report	Kashiwabara and Ota ¹⁰
1	Case report	Tomsic and Sifrer ¹¹

Table 3 Case reports of antisynthetase syndrome presenting as interstitial lung disease (ILD) without myositis

Number of cases	Type of study	Reference
4	Case series	Sauty <i>et al</i> ¹²
10	Case series	Friedman <i>et al</i> ¹³
1	Case report	Plastiras <i>et al</i> ¹⁵
1	Case report	Sundaragiri <i>et al</i> ¹⁶
1	Case report	Kiely <i>et al</i> ¹⁷
6	Retrospective study	Koreeda <i>et al</i> ¹⁸
28	Retrospective multicentre study	Cavagna <i>et al</i> ¹⁹
10	Retrospective multicentre study	Tillie-Leblond <i>et al</i> ¹⁴

antisynthetase antibodies and eight different ARS have been identified to date: anti-Jo-1 (most common), anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS, anti-ZO and anti-Ha.^{1–4}

The exact mechanisms leading to the disorder are not known. Viral infections are thought to promote the formation of antisynthetase antibodies. HLA-DRB1*0301, DQA1*0501 and DQB1*0201 genes are risk factors for the development of anti-Jo-1+AS syndrome.¹ Although a substantial part of the genetic risk for developing myositis and various phenotypes lies within the major histocompatibility complex, recent research suggests that genetic regions outside of the major histocompatibility complex are also potentially involved in conferring IIM disease susceptibility.

The syndrome is generally considered present in patients with an antisynthetase antibody plus one or two of the following features, which are elements of the syndrome: ILD, inflammatory myopathy and inflammatory polyarthritis. Raynaud's phenomenon, mechanic's hands and fever are other features that are less prevalent clinical findings. The clinical presentation of anti-Jo-1 ASS varies greatly, with cases presenting without the classic triad and hence making it difficult to define specific diagnostic criteria.^{1–3} In these patients, the other clinical features may evolve during follow-up.

ILD is frequent in ASS and reported in 60–70% of cases and drives the prognosis and may precede myositis in 7–33% of the cases.⁴ Lung biopsies obtained show four histological patterns that may correspond to different stages of pulmonary fibrosis and include: organising pneumonia, NSIP, usual interstitial pneumonia (UIP) and NSIP with fibrosis.¹ Furthermore, 5–8% of cases of ASS manifest with other connective tissue disease, including rheumatoid arthritis, lupus, scleroderma and Sjogren's syndrome.^{1–3} The presence of RO-52 antibodies in ASS indicates poor prognosis.¹

In our patient, ASS diagnosis was based on the presence of the anti-Jo-1 antibodies in the serum coupled with ILD seen on

the CT scan of the chest that was confirmed on the lung biopsy to be NSIP with fibrosis. Our patient also had serum antibodies positive for SS-A(Ro), CCP, RNP and ANA which are seen in 5–8% of the ASS patients but have no prognostic significance.^{1–4}

ARDS is a rare presentation of ASS, reported in dermatomyositis (table 2).^{5–11} Clawson and Oddis⁵ reported ARDS in three cases at initial presentation and during the course of ASS. All had myositis features at the time of presentation.

Lung disease can predominate or can be the sole manifestation in the absence of clinically apparent myositis. Case reports have described ILD in patients with anti-Jo-1 antibodies without myositis (table 3) but none presented as ARDS.^{12–19} Sauty *et al*¹² reported NSIP in lung biopsies and anti-Jo-1 antibodies without myositis in four patients, Friedman *et al*¹³ identified 10 patients with antisynthetase antibodies with ILD and no myositis and Tillie-Leblond *et al*¹⁴ described two-thirds of the 32 patient with ASS presenting without myositis at the time of diagnosis, but more than half of the patients developed myositis during follow-up.

Learning points

To the best of our knowledge, here we described a first case of antisynthetase syndrome (ASS) presenting as acute respiratory distress syndrome in a patient who had no myositis features at the onset. Our patient was diagnosed with ASS based on antibody profile and lung biopsy findings. There was at least 2 weeks delay between the acute presentation and diagnosis as the patient showed no muscle weakness at the onset or previous history of lung disease. In the absence of clinically or electromyographically apparent myositis, no muscle biopsy was performed. We conclude from this case that:

- ▶ Anti-Jo-1 antibody search should not be restricted to patients with myositis but also performed in cases of isolated interstitial lung disease (ILD) or patients presenting with acute respiratory failure as the identification of anti-Jo-1 is relevant because of its therapeutic and prognostic significance.
- ▶ Lung disease can predominate or can be the sole manifestation in the absence of clinically apparent myositis, and patients can be misdiagnosed as having idiopathic pulmonary fibrosis when underlying ASS is not suspected. This distinction is important because these conditions differ in their pathology and treatment.
- ▶ In cases of isolated ILD associated with antisynthetase antibodies, one cannot exclude the possibility of subclinical muscle involvement as myositis may have been prevented or controlled well enough by drugs to escape detection. It is also difficult to identify myositis during the follow-up period when corticosteroid treatment may also have induced myopathy.
- ▶ In this case, determining the type of ILD was important because the type of ILD influences treatment and prognosis. NSIP due to underlying cause has better prognosis compared with idiopathic NSIP. Owing to the diagnosis of ASS, a second agent was added early in the course, given the high frequency of progressive disease.

Contributors SP and VKK were involved in the patient care. SS and SM helped writing the case report.

Competing interests None declared.

Patient consent Obtained.

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