A case of antisynthetase syndrome presenting solely with life-threatening interstitial lung disease

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ABSTRACT

A previously fit and well 38-year-old man presented during the COVID-19 pandemic with dyspnoea, cough and palpitations. C-reactive protein was elevated and chest X-ray demonstrated bilateral lower zone consolidation. SARS CoV-2 swab was negative. He was diagnosed with community-acquired pneumonia and treated with oral antibiotics. He developed severe type 1 respiratory failure and was admitted to the high-dependency unit for non-invasive ventilation. CTPA was negative for pulmonary embolism, instead demonstrating bilateral organising pneumonia. Empirical treatment for swab-negative COVID-19 pneumonitis was started; however, further deterioration ensued and prompted intubation and ventilation. Microbiological testing did not yield any positive results, thereby raising suspicion for the presence of an autoimmune disease. Pulsed intravenous methylprednisolone was administered with good effect. ENA screen was positive for anti-Jo1 and myositis-specific autoantibodies were positive for Ro-52, Ku and PL-12. The patient was extubated and did not exhibit any muscle weakness on clinical examination. Creatine kinase was only mildly elevated. He was diagnosed with amyopathic antisynthetase syndrome - frequently considered as a form of idiopathic inflammatory myopathy (IIM) - and treated with further intravenous methylprednisolone and cyclophosphamide. Oxygen therapy was gradually weaned and the patient discharged on mycophenolate mofetil and a weaning course of oral steroids.

KEYWORDS: interstitial lung disease, myositis, idiopathic inflammatory myopathy, antisynthetase syndrome

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Introduction

A 38-year-old black British man self-presented to the emergency department with a 1-week history of cough and a 2-day history of palpitations and dyspnoea. There was no fever, chest pain, collapse or haemoptysis; no significant past medical history and no drug history. He was employed as a software engineer and had received his second COVID-19 vaccination a few months prior to presentation. The patient denied any history of smoking, recreational drug use, unwell contacts or recent travel.

Initial observations were: SpO_2 85% on room air, RR 18, T 36.4, BP 141/83 and HR 127. Chest auscultation revealed bibasal crepitations. Heart sounds were normal and there were no peripheral signs of heart failure or deep venous thrombosis. Abdominal and neurological examination was unremarkable.

Full blood count revealed haemoglobin 143 g/L, white cell count 19.37 $\times$ 10^9/L (neutrophils 14.78 $\times$ 10^9/L, lymphocytes 2.61 $\times$ 10^9/L) and platelets 327 $\times$ 10^9/L. C-reactive protein was elevated at 61.7 mg/L. Liver function tests and renal function were normal.

12-lead electrocardiogram demonstrated a sinus tachycardia and bilateral consolidation was apparent on chest radiograph. Rapid respiratory PCR was negative for SARS CoV-2, influenza and respiratory syncytial virus.

An initial diagnosis of community-acquired pneumonia was made and the patient was treated with doxycycline.

Case progression

Over the ensuing 12 hours, the patient deteriorated, eventually requiring 15L O_2 via NRB to maintain SpO_2 93%. CTPA was negative for pulmonary embolism and instead revealed bilateral organising pneumonia.

He was diagnosed with COVID-19 pneumonitis and commenced on oral dexamethasone and doxycycline, intravenous ceftriaxone and treatment dose low-molecular weight heparin. CPAP was started and the patient was transferred to the high-dependency unit (HDU). Repeat SARS CoV-2 swab was again negative.

The patient was initially managed with CPAP / Optiflow. Atypical pneumonia screen was sent and doxycycline was changed to clarithromycin. After initial improvement and step-down from HDU, he again deteriorated with recurrence of type 1 respiratory failure necessitating admission to the intensive care unit (ICU) where this time he was intubated and ventilated. Further SARS-CoV-2 swabs were negative, as was the atypical pneumonia screen and repeated urine, sputum and blood cultures, ultimately raising suspicion for an autoimmune disease. Antibiotics were escalated to tazocin and the patient pulsed with IV methylprednisolone (IVMP) 500mg once daily for 3 days. Successful extubation to CPAP / Optiflow occurred after 48 hours, with C-reactive protein improving from 148.2 on re-admission to ICU to 9.4 mg/L.

Further biochemistry, immunology, virology and imaging was requested; ESR 25 mm/hr, CK 360 IU/L, ANA and ANCA screens

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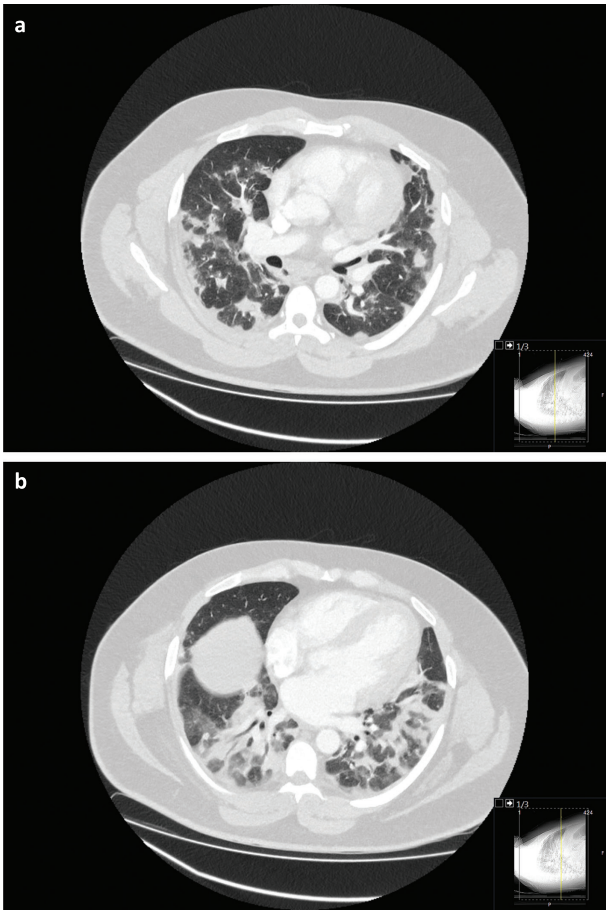

Fig 1. Lung windows from CTPA, in both sagittal (a) and coronal (b) planes, demonstrating widespread patchy subsegmental consolidation within both lungs. The changes are confluent within both lower lobes.

both negative, viral hepatitis and HIV screens negative and bedside echocardiography was entirely normal.

Diagnosis

ENA screen was positive for Jo-1 antibody. Myositis-specific autoantibodies were positive for Ro-52, Ku and PL-12 in addition to Jo-1, and a diagnosis of antisynthetase syndrome was made.

Initial management & prognosis

IVMP was administered again (this time at 1 g once daily for 3 days) and EUVAS protocol cyclophosphamide (CYC) was started. The prognosis was felt to be poor in this instance in view of the diagnostic delay and florid, aggressive pulmonary disease.

Outcome

Fortunately, this patient responded well to immunosuppression with IVMP and CYC, and was successfully weaned off oxygen therapy following his third cycle of IV CYC, with weaning oral prednisolone. Repeat imaging of the chest prior to discharge confirmed radiological improvement. Following his fourth cycle of IV cyclophosphamide he was commenced on oral mycophenolate mofetil (MMF) 3 mg/kg with 5 mg oral prednisolone.

While the patient's respiratory condition has improved, following discharge he did develop myositis with CK 5,023 IU/L.

Discussion

Antisynthetase syndrome is a rare autoimmune condition that is frequently considered a separate form of idiopathic inflammatory myopathy (IIM). It is characterised by interstitial lung disease (ILD), myositis and arthritis in the presence of an antibody, or antibodies, directed against aminoacyl-tRNA synthetases (ARSs). Other clinical features can include mechanic's hands, Raynaud's phenomenon and calcinosis.

As in this case, not all those with IIM have discernible muscle weakness. These patients are said to be amyopathic. In 2017, the EULAR / ACR classification criteria for adult IIM outlined four major subgroups: polymyositis (PM) including immune-mediated necrotising myopathy (IMNM), dermatomyositis (DM), amyopathic dermatomyositis (ADM) and inclusion body myositis (IBM)[1] This set of criteria replaced the 1975 Bohan and Peter criteria for PM and DM.[2]

The discovery of myositis-specific autoantibodies (MSAs) has provided clinicians with the ability to diagnosis IIM subtype in a way that was previously not possible. For example, detection of anti-SRP antibody is highly specific for IMNM. Similarly, anti-TIF-1 antibody is associated with an increased risk of underling malignancy.[3]

The antisynthetase autoantibodies include anti-Jo1, anti-EJ, anti-OJ, anti-PL7 and anti-PL12, among others. Each of these autoantibodies is associated with varying clinical phenotypes across ethnicities. Anti-Jo1 (directed against histidyl-tRNA synthetase) is the antisynthetase autoantibody most frequently identified in cases of antisynthetase syndrome.

Again, as described in this case, not all patients with IIM have elevated muscle enzymes at presentation. In antisynthetase syndrome-related ILD, high-resolution computed tomography (HRCT) of the chest most commonly reveals non-specific interstitial pneumonia (NSIP), organising pneumonia (OP) or a combination of the two.

High dose corticosteroids (prednisolone 1 mg/kg/day or methylprednisolone 1g IV once daily for 3 days) are the cornerstone of therapy in antisynthetase syndrome. However, treatment is not standardised and takes into account the organ systems involved (muscles, joints, skin and lungs), as well as the rate and severity of damage to these organs.

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as azathioprine and mycophenolate mofetil, or calcineurin inhibitors such as tacrolimus, can be started contemporaneously to reduce relapse whilst tapering steroids.

Life-threatening ILD often responds well to further immunosuppression with cyclophosphamide. IVIg has an established role in treatment induction for severe or refractory disease, and there is growing interest in the role of Rituximab. Patients with ILD refractory to these treatments may be considered for lung transplantation, and physiotherapy and pulmonary rehabilitation must always be remembered as key non-pharmacological treatments.[4]

Key learning points

- Antisynthetase syndrome is a form of idiopathic inflammatory myopathy (IIM) which can present solely with rapidly progressive, life-threatening interstitial lung disease.

- The clinical manifestation of IIM is extremely varied; not all forms of IIM present with muscle weakness and/or elevated CK, though this can develop later in the disease course.
- Idiopathic ILD should trigger evaluation for non-infective diagnoses including idiopathic inflammatory myopathy (IIM) and connective tissue disease (CTD).
- Myositis-specific antibodies (MSAs) are essential in the investigation of patients with suspected IIM.
- Treatment is with immunosuppression; corticosteroids are the mainstay of treatment, with a role for early introduction of DMARDs and use of cyclophosphamide in life-threatening disease. ■

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