CASE REPORT

Fatal cardiac involvement complicating antisynthetase syndrome

Stefen Brady,¹ Sunil Melath,² Renata S Scalco,¹ Henry Penn²

¹Department of Neuropathology, MRC Centre for Neuromuscular Diseases, London, UK
²Department of Rheumatology, Northwick Park Hospital, London, UK

Correspondence to
 Dr Stefen Brady,
 stefenbrady@nhs.net

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SUMMARY

A 35-year-old Afro-Caribbean woman presented with dyspnoea, urticarial rash and myalgia 1 month after treatment for a community-acquired respiratory tract infection. Investigations revealed raised antisynthetase antibodies, lung fibrosis and an inflammatory myopathy. The patient was diagnosed with antisynthetase syndrome (ASS) and started on immunosuppressive medication. Despite treatment she died 4 weeks after presentation from a fulminant cardiomyopathy. ASS is a rare condition and is not typically associated with a cardiomyopathy. This case report intends to raise awareness that cardiomyopathy is a potentially fatal complication of ASS.

BACKGROUND

Antisynthetase syndrome (ASS) is a rare autoimmune disorder characterised by autoantibodies against aminoacyl tRNA synthetases (ARS) and clinical features including interstitial lung disease, dermatomyositis (DM) or polymyositis (PM), fever, non-erosive arthritis, Raynaud's phenomenon, 'mechanic's hands' and sometimes a DM-rash. ARS are enzymes which catalyse the binding between corresponding amino acids and tRNA. To date, antibodies have been described to eight ARS¹ and there is evidence that different ARS antibodies are associated with different clinical manifestations and disease course.² ASS is not typically associated with cardiac disease and to the best of our knowledge, there have been no reported cases of a fatal cardiomyopathy in ASS.

CASE PRESENTATION

A 35-year-old Afro-Caribbean woman presented to our hospital with dyspnoea, fever, impaired mobility and a rash. One month earlier she had received oral antibiotics for a presumed chest infection. Two days after starting antibiotic treatment she developed a pruritic macular rash affecting her trunk and legs. This was followed several days later by joint swelling, myalgia and dyspnoea. She had long-standing mild Raynaud's phenomenon. Family history was unremarkable. She was a non-smoker and did not drink alcohol.

On initial assessment, she was afebrile, normotensive and tachycardic (100 bpm), but not tachypnoeic. Oxygen saturations were 98–99% on room air. Examination revealed fissuring of the distal digital skin pads—'mechanic's hands', active Raynaud's phenomenon, dilated nail-fold capillaries and an urticarial rash covering her thighs. Bilateral fine basal crackles were heard on

auscultation of the lungs. Cardiac and abdominal examinations were unremarkable. Joint examination revealed bilateral knee effusions and wrist synovitis. Mild bilateral proximal lower limb weakness was noted on neurological examination.

INVESTIGATIONS

Investigations revealed that the serum creatine kinase (CK) level was elevated at 9900 IU/L (normal range (NR) 25–200 IU/L). C reactive protein was 43 mg/L (NR 0–5.0 mg/L) and erythrocyte sedimentation rate was 114 mm/h. White cell count was $12.2 \times 10^9/L$ (NR $3\text{--}10 \times 10^9/L$) with a neutrophilia of $10.2 \times 10^9/L$. Moderate haematuria and proteinuria were present on urinalysis and urinary protein:creatinine ratio was elevated at 55 (NR <30). Antinuclear antibody (1:80, speckled pattern) and anti-Ro and anti-La antibodies were positive. Anti-glycyl (anti-EJ) ARS antibodies were positive. Troponin T (TnT), complement, antineutrophil cytoplasmic antibody, anticyclic citrullinated peptide and rheumatoid factor were normal. ECG showed sinus tachycardia. High-resolution CT of the chest showed bilateral basal fibrosis. Electromyography was myopathic with prominent spontaneous activity. MRI of the legs revealed oedema in the quadriceps (figure 1), peroneal and anterior tibial muscles bilaterally.

Skin biopsy revealed changes consistent with a drug reaction (mild dermis perivascular infiltrate consisting of lymphocytes, histiocytes and scattered eosinophils). Muscle biopsy of the left vastus lateralis demonstrated variation in fibre size (20–90 μm), frequent atrophic, necrotic and regenerating fibres, many of which were distributed in a perifascicular pattern (figure 2A, B). A small number of fibres contained vacuoles, which were not rimmed. There was a moderate perimysial and perivascular inflammatory infiltrate. A Gomori trichrome preparation revealed some fragmentation of the perimysium (figure 2C). There was no disturbance of the internal architecture of fibres. There was increased perimysial alkaline phosphatase activity (figure 2D). Mitochondrial, glycogen and lipid staining were normal. Immunohistochemical staining demonstrated increased numbers of endomysial and perimysial CD8 positive T-cells (figure 2E). CD68 immunoreactive macrophages were frequent in the endomysium and perimysial connective tissue. CD20 positive B-cells were rare. Major histocompatibility complex class I (MHC class I) expression was increased at the sarcolemma and within the sarcoplasm of most fibres without emphasis in the perifascicular areas. Complement membrane attack

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Figure 1 Axial short tau inversion recovery sequence MRI of thighs showing increased signal in the quadriceps bilaterally consistent with oedema.

complex (MAC) was increased in necrotic fibres and around the sarcolemmal in some fibres (figure 2F). There was no capillary MAC staining. The pathological features including abnormal perifascicular fibres, increased MHC class I expression, endomysial and perimysial inflammatory infiltrate, mild fragmentation of perimysial connective tissue and increased perimysial alkaline phosphatase activity are consistent with an inflammatory myopathy and categorised as an immune-mediated myopathy with perimysial pathology which is associated with antibodies to ARS.³

Figure 2 H&E staining shows increased variation in fibre size, necrotic and regenerating fibres in addition to a perimysial and endomysial inflammatory infiltrate (A). Perifascicular atrophy observed on H&E staining is emphasised by neonatal myosin immunohistochemistry (B). Gomori trichrome preparation reveals fragmentation of the perimysium and necrotic fibres (C). Alkaline phosphatase staining is increased in the perimysium (D). Inflammatory cells are seen in the endomysium and perimysium, often with a perivascular distribution and are predominantly CD8 positive T-cells (E). Complement membrane attack complex (MAC) highlights necrotic fibres and is increased around the sarcolemmal in some fibres; however, there is no capillary MAC staining as is sometimes observed in dermatomyositis (F). The bar in A represents 100 μ m in F; 50 μ m in A, B, D and E; and 25 μ m in C.

TREATMENT

A diagnosis of ASS was made and 14 days after admission oral prednisolone was started at a dose of 40 mg daily. Despite treatment, the patient experienced intermittent fevers, worsening proximal weakness and the CK rose to 19 000 IU/L. Oral steroids were substituted with intravenous methylprednisolone and intravenous immunoglobulin. At this point the patient reported presyncopal episodes. Investigations revealed a raised TnT of 0.25 μ g/L (NR <0.1 μ g/L). ECG showed sinus tachycardia. Echocardiography was normal. Five days later, TnT was 4.00 μ g/L and repeat echocardiography revealed bilateral atrial and ventricular dilation consistent with myocarditis. Left ventricular ejection fraction was reduced at 40% and pulmonary arterial pressure was elevated at 39 mm Hg. Owing to the patient's deteriorating clinical condition, intravenous cyclophosphamide was started.

OUTCOME AND FOLLOW-UP

Despite continued immunosuppressive treatment, the patient developed cardiogenic shock complicated by trifascicular block and acute renal failure. She received intensive support including inotropes and cardiac pacing; however, she suffered a fatal cardiac arrest 25 days after admission.

DISCUSSION

Clinical and pathological studies have shown that cardiac involvement is not uncommon in other inflammatory

myopathies such as DM and PM and is responsible for significant morbidity and mortality.^{4 5} Cardiac involvement in DM and PM may be subclinical⁶ and how best to diagnose and treat it in inflammatory myopathies is uncertain. By contrast, primary cardiac involvement is relatively unknown in ASS and severe cardiomyopathy has not been reported. However, cardiac disease in ASS may have gone unnoticed if it is usually subclinical or it may have been overlooked because of the rarity of ASS. Whether earlier initiation of aggressive immunosuppressive

therapy would have altered the outcome for our patient is unknown. Given the potentially devastating outcome, we wish to raise awareness among physicians that severe cardiac involvement may occur in patients with ASS.

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Competing interests None.

Patient consent Obtained.

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Learning points

- ▶ Antisynthetase syndrome (ASS) is characterised by antibodies against aminoacyl tRNA synthetases (ARS) and clinical features including interstitial lung disease, dermatomyositis or polymyositis, fever, non-erosive arthritis, Raynaud's phenomenon, 'mechanic's hands' and rash.
- ▶ Different ARS antibodies may be associated with different clinical manifestations and disease course.
- ▶ Consider ASS in inflammatory myopathies with marked perimysial pathology.
- ▶ Severe cardiac disease may occur in association with ASS.

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