Drug-induced antisynthetase syndrome

DR Thickett, AB Millar

Summary
We present a case of antisynthetase syndrome whose predominant feature was fibrosing alveolitis and which may have been drug-induced. This responded well to steroids and cyclophosphamide.

Keywords: antisynthetase syndrome, valsartan

In the idiopathic inflammatory myopathies (eg, polymyositis), interstitial lung disease is associated with autoantibodies directed against aminoacyl tRNA synthetases. The most frequent, Jo-1, is found in approximately 20% of myositis patients.

The antisynthetase syndrome consists of myositis, arthritis, Raynauds phenomenon, fever, skin lesions including 'mechanic’s finger', and interstitial lung disease. The frequency of pulmonary fibrosis varies between 40–100%, while myositis is present in 86–100%. Herein we describe a case of antisynthetase syndrome without myositis.

Case report

A 68-year-old man presented with worsening shortness of breath upon exertion. He had started the angiotensin II receptor antagonist, valsartan, as part of a drug trial two months prior to presentation. The onset of symptoms was coincident with starting the trial drug. The patient had a dry cough, arthralgia of the wrists, and had noticed a rash.

Upon admission he was tachypnoeic (respiratory rate 24 breaths/min). Chest auscultation revealed fine inspiratory crepitations to midzone bilaterally. Cardiovascular and abdominal examination was unremarkable.

There was no muscular weakness. He had tenderness of wrists and metacarpophalangeal joints bilaterally. There were scaly erythematous macules upon the extensor surfaces of the elbows (figure 1), and palmar aspects of the fingers. The skin over the lateral aspects of the fingers was fissured and rough with hyperkeratosis and scaling (figure 2). The nail-fold capillaries were dilated and distorted.

Laboratory investigations revealed haemoglobin 16.3 g/dl, white cell count 11.6 x 10^9/l and platelets 366 x 10^9/l; creatinine kinase was normal as were renal and liver function tests. There was no proteinuria or haematuria and blood cultures were negative. A chest X-ray showed bilateral lower zone reticular shadowing. Pulmonary function tests revealed a restrictive defect with reduced transfer factor.

Blood gases on air were pH 7.4, pO_2 _7.79 kPa, pCO_2 _4.8 kPa, oxygen saturation 91%. Bronchoalveolar lavage revealed a neutrophilia of 40% with 60% macrophages. A transbronchial biopsy showed active fibrosing alveolitis with focal fibrotic thickening and a patchy lymphocytic infiltration. A skin biopsy of the fingers revealed the histological pattern of mechanic’s finger.

The autoimmune profile showed a negative ENA, rheumatoid factor, and ANCA, with

![Figure 1](image1.png) Hyperkeratotic lesion of elbow

![Figure 2](image2.png) Mechanic’s finger

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Table 1 Respiratory function tests

<table>
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<th>Date</th>
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<th>17/11/94</th>
<th>6/1/95</th>
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<tr>
<td>FEV₁</td>
<td>1.8</td>
<td>2.09</td>
<td>2.28</td>
<td>2.52</td>
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<tr>
<td>FVC</td>
<td>1.85</td>
<td>2.28</td>
<td>2.6</td>
<td>2.82</td>
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<tr>
<td>FEV₁/FVC (%)</td>
<td>97</td>
<td>92</td>
<td>87</td>
<td>87</td>
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<tr>
<td>PEF</td>
<td>500</td>
<td>540</td>
<td>590</td>
<td>625</td>
</tr>
<tr>
<td>tCO (%) pred*</td>
<td>3.03 (34)</td>
<td>3.42 (38)</td>
<td>3.85 (43)</td>
<td>4.08 (46)</td>
</tr>
<tr>
<td>kCO (%) pred**</td>
<td>1.02 (77)</td>
<td>1.15 (87)</td>
<td>1.2 (90)</td>
<td>1.15 (87)</td>
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</tbody>
</table>

*tlCO= CO transfer factor (mmol.min⁻¹.kPa⁻¹)
**kCO= transfer coefficient (tCO/Vs min⁻¹.kPa⁻¹.l⁻¹)

Table 2 Arterial blood gas measurements on air

<table>
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<tr>
<th>Date</th>
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<th>12/8/94</th>
<th>31/8/94*</th>
<th>16/9/94</th>
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<tr>
<td>pO₂</td>
<td>7.79</td>
<td>8.23</td>
<td>5.86</td>
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<td>11.58</td>
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<tr>
<td>pCO₂</td>
<td>4.83</td>
<td>4.75</td>
<td>4.79</td>
<td>5.13</td>
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<tr>
<td>pH</td>
<td>7.41</td>
<td>7.43</td>
<td>7.43</td>
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</tbody>
</table>

*Cyclophosphamide and methylprednisolone commenced for three cycles two weeks apart; **started prednisolone 40 mg orally daily continuously.

normal complement levels. Hep2 staining was homogenous at 1:160 dilution. *S-Methionine-labelled protein immunoprecipitation and gel electrophoresis subsequently proved negative for the characterised antisynthetase antibodies, including Jo-1, PL7, and PL12. There was, however, a low titre of anticytoskeletal antibodies which disappeared after 10 months of treatment.

Treatment was initiated with 1 g methylprednisolone intravenously (iv) once daily for three days followed by prednisolone 60 mg orally once daily. After an initial minor clinical improvement, the patient’s condition continued to deteriorate (table 1). Pulse iv cyclophosphamide at 15 mg/kg, with 1 g methylprednisolone iv every two weeks was therefore started. There was a good response to three cycles of treatment (tables 1 and 2). The patient was transferred to 40 mg prednisolone daily. Eight months after presentation he remains well with significantly improved blood gases, and pulmonary function tests (tables 1 and 2). He is on a reducing regime of prednisolone.

Discussion

This patient presented with dermatomyositis-like skin changes and severe interstitial lung disease. The presence of the mechanic’s finger skin lesions suggested an antisynthetase syndrome despite the absence of myositis.6 We were unable to confirm this serologically. Interestingly, the features of mechanic’s finger have previously only been described with overt myositis.7 We believe that this is the first case report of a patient with mechanic’s finger in the absence of clinical myositis.

The temporal relationship between the onset of symptoms and initiation of treatment with valsartan, raises the possibility of a drug-induced or triggered phenomenon. Proving a pneumonitis is drug-induced is only possible when strict criteria are met.6 Although this case does not meet all these criteria, the strong clinical impression of an association between valsartan treatment and this life-threatening pneumonitis is a cause for concern. Since valsartan is an experimental drug, we suggest there should be heightened vigilance for similar problems in the future.

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