CASE REPORT

Inflammatory myopathy and interstitial lung disease in antisynthetase syndrome with PL-7 antibody

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SUMMARY

We report a case of a 72-year-old Caucasian woman with PL-7 positive antisynthetase syndrome. Clinical presentation included interstitial lung disease, myositis, 'mechanic's hands' and dysphagia. As lung injury was the main concern, treatment consisted of prednisolone and cyclophosphamide. Complete remission with reversal of pulmonary damage was achieved, as reported by CT scan, pulmonary function tests and functional status.

BACKGROUND

This paper describes a case of a new onset of hypoxaemia, lung disease and muscle weakness in a 72-year-old woman whose symptoms did not respond to antibiotherapy.

CASE PRESENTATION

A 72-year-old Caucasian woman with no previous significant medical history, medicated with simvastatin 40 mg, omeprazole 20 mg and diazepam 10 mg, presented to her primary care physician with fever, dyspnoea, productive cough and asthenia. One month after treatment with azithromycin and amoxicillin/clavulanic acid with no improvement the patient was admitted to the hospital for investigation.

On admission, the patient presented with fever (38°C), tachypnoea (30 breaths/min), hypoxaemia (89% oxygen saturation on room air) and bibasilar rales. She had peripheral oedema particularly in inferior limbs and hands.

During hospitalisation the patient developed proximal weakness and had difficulty rising from a chair or raising her arms; she displayed mild oropharyngeal dysphagia for solids. The skin on her hands were thick with fissures on the lateral and palmar surfaces of the fingers.

INVESTIGATIONS

Relevant laboratory findings included a 10-fold rise in creatine kinase (1792 IU/L) and myoglobin (1107 IU/L), with moderate rise in lactate dehydrogenases and transaminases. The blood cell count was normal and there was no renal injury or thyroid dysfunction.

No relevant changes were observable in the ECG.

Echocardiogram revealed mild mitral stenosis, with no left atrial enlargement and normal left ventricular dimensions and systolic function. Right cavities were not dilated, and right ventricular systolic function was preserved. There was no evidence of pulmonary hypertension or pericardial infusion.

Chest radiography showed interstitial infiltrate in the lower third of both lungs (figure 1).

CT scan showed bronchiectasis, ground-glass opacities, interstitial fibrosis with honeycombing pattern and pleural thickening in the lower half of both lungs (figure 2).

Blood cultures were persistently negative. All serological tests were negative, including coxsackievirus, adenovirus, cytomegalovirus, HIV and *Coxiella burnetii*.

With these results an infectious aetiology seemed less likely and diagnostic reasoning focused on an autoimmune systemic disease, mainly due to lung injury, myopathy and thickened, hyperkeratotic hands ('mechanic's hands').

Antinuclear antibodies were positive (titre 1/160) with ELISA specificity for anti-Ro52 and anti-PL7. Other immunological tests were negative, including anti-Jo-1, Scl-70, dsDNA, Sm, SSB, RNP, ANCA and rheumatoid factor.

Nailfold capillaroscopy presented reduced capillary density, with multiple dysmorphias (crossings, tortuosity and ramifications), enlarged capillaries (one megacapillary) and microhaemorrhages (figure 3). Some capillaries had a rosary-like appearance and circulation was slow.

Electromyography revealed signs of muscular fibre necrosis and spontaneous activity. In this clinical context such findings were consistent with inflammatory muscle disease. According to these results the patient had a muscle biopsy, which confirmed a primary inflammatory myopathy, showing atrophic and necrotic fibres, sarcoplasm reduction and miofagocytosis. Immunocytochemical test for major histocompatibility antigens was positive in the sarcolemma of all muscular fibres.

Figure 1 Chest radiography: interstitial infiltrate in the lower third of both lungs.

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Figure 2 CT scan: bronchiectasis, ground-glass opacities, interstitial fibrosis with honeycombing pattern and pleural thickening.

Pulmonary function tests demonstrated a restrictive pattern: forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) 75.9%, total lung capacity (TLC) 3.21 L (62%), residual volume (RV) 1.27 L (59%) and a mild decrease in diffusing capacity (DLCO) 77.9%.

DIFFERENTIAL DIAGNOSIS

The first diagnostic hypothesis was infection due to fever, predominant pulmonary symptoms and imaging findings. There was, however, no improvement after antibiotic treatment, with a progressive deterioration of clinical status and blood cultures remaining negative. After that, less frequent pathogens were searched. Even with the absence of epidemiological context, the clinical picture of lung injury, myopathy and hepatic involvement made Q fever a possible diagnosis. This was refuted by a negative serology for *C. burnetii*. Other serological tests for atypical pneumonia agents were also negative.

There were likewise no environmental or occupational inhalation exposures that could cause lung damage.

Considering the myopathic involvement, it was important to exclude hypothyroidism as the cause of proximal weakness by laboratory analysis. The patient was medicated with a HMG-CoA reductase inhibitor, which can cause myopathy in approximately 0.1% of patients. However, this side effect did not explain the pulmonary injury, so that hypothesis was discarded.

Considering the multisystem involvement, an autoimmune disease seemed more likely. The clinical picture fitted in the diagnosis of antisynthetase syndrome (ASS), as this entity is characterised by polymyositis and interstitial lung disease (ILD). The patient presented severe lung injury characterised by interstitial fibrosis and a restrictive pattern in pulmonary function tests. This was deemed relevant since lung disease usually dominates the clinical picture and determines the prognosis.

Figure 3 Nailfold capillaroscopy: reduced capillary density with enlarged capillaries and one megacapillary (arrow).

Pulmonary injury was accompanied by inflammatory myopathy, which caused proximal weakness. Apart from the rise in creatine kinase and myoglobin, myositis is also associated with a rise in lactate dehydrogenase and transaminases, as observed in this case. Muscle disease may affect the pharynx and upper oesophagus causing dysphagia.

In addition to both pulmonary and myopathic involvement, several other signals like fever and ‘mechanic’s hands’ are also associated with ASS.

Immunological tests were consistent with clinical findings, with positive anti-PL-7 antibodies.

This diagnosis was substantiated by the electromyography, muscular biopsy and nailfold capillaroscopy.

TREATMENT

The patient was started on prednisolone (0.7 mg/kg/day) and intermittent intravenous cyclophosphamide (700 mg/m² every 30 days for 6 months), with a rapid improvement in respiratory symptoms and muscle weakness in the first 2 weeks of treatment.

Liver tests showed worsening in the beginning of therapy, leading to a reduction by 25% of the cyclophosphamide dose. The laboratory findings returned to normal with continuation of treatment.

Prednisolone was tapered to 7.5 mg/day at 6 months, keeping a maintenance therapy with azathioprine (3 mg/kg/day).

OUTCOME AND FOLLOW-UP

By the end of the cyclophosphamide treatment the disease was in clinical remission. CT scan documented almost complete recovery of lung disease, with regression of ground-glass opacities and interstitial pattern (figure 4). Pulmonary function tests demonstrated a mild restrictive pattern, with improvement of FEV1/FVC (84.4%), TLC 4.27 L (88%) and RV 2.04 L (94%) with normal DLCO 88.6%. Creatine kinase returned to a normal value (61 U/L).

DISCUSSION

ASS is an autoimmune disease characterised by inflammatory myopathy in combination with ILD. Other typical features are fever, arthritis or arthralgias, Raynaud’s phenomenon, ‘mechanic’s hands’ (thickened skin along the fingers’ lateral surfaces with dry cracking and fissuring) and oesophageal dysmotility.^{1–4} It is associated with the presence of antibodies against aminoacyl-tRNA synthetases. The most frequent is the antihistidyl-tRNA synthetase (anti-Jo-1), found in approximately 30% of patients with myositis.^{1 5} The other less common antibodies are antithreonyl (PL-7), antialanyl (PL-12), antiisoleucyl (OJ) antiglycyl (EJ), antiasparaginyl (anti-KS) and antiphenylalanyl (anti-ZO). PL-7 is detected in only 2–5% of cases.^{1 5}

There is a variety of disease phenotypes that appear to be related to antisynthetase antibodies. The major determinant of

Figure 4 CT scan after conclusion of treatment with cyclophosphamide: marked regression of ground-glass opacities and interstitial pattern.

morbidity and mortality is the severity of lung disease, and there is no correlation between severity of lung disease and of myositis.

ILD can dominate the clinical picture, particularly in the presence of non-Jo-1 antisynthetase antibodies. It may also be the presenting feature and it is, in fact, more common that ILD precedes myositis.^{3 6} In patients with anti-PL-7, myositis and arthritis may be less frequent and milder than in those with anti-Jo-1.^{3 7} In this context it is important to search for anti-PL-7 and other antisynthetase antibodies in patients with ILD to detect an underlying ASS, since this finding influences the treatment and prognosis.^{4 8 9} In a recent study, anti-PL-7 antibodies appear to be a positive prognostic factor of myositis in ASS.⁴ Antibodies overlapping is also frequent, particularly anti-Ro52 and antisynthetase antibodies, with this conjugation being associated with a more severe ILD.^{3 8}

In ASS, ILD may present as one of the following three patterns: rapidly progressive acute, subacute or chronic progressive fibrosing. The most common clinical presentation is a gradual progression of non-productive cough, dyspnoea and decrease in functional capacity.^{3 4 9}

A CT scan can show fibrosis of the pulmonary interstitium, bronchiectasis, linear opacities, ground-glass opacities and honeycombing pattern.^{1 2 4 5} Lung biopsy is not necessary when a typical pattern is seen on CT scan.^{4 10}

Pulmonary function tests typically demonstrated a restrictive pattern (reduction of TLC, FVC, FEV1 and RV with an elevated FEV1:FVC ratio) and a decrease of DLCO.^{3 5 6 10}

In patients with idiopathic inflammatory myopathy, nailfold capillaroscopy can show lower capillary density, higher capillary dimensions, arborised capillaries, avascular areas and microhaemorrhages.^{11 12} This finding and ILD may be related, suggesting that these are different manifestations of a common pathway.¹²

Muscular biopsy can show inflammatory myopathy, particularly in perimysium and atrophic perifascicular tissue.²

Glucocorticoids are the first line of treatment. In severe cases an immunosuppressive agent should be added, particularly if there is progressive or severe ILD.

Experience using cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, methotrexate and rituximab have been reported.^{2 3 9} As there are no controlled clinical trials the level of evidence for choosing a treatment remains low.

ILD is the main prognostic factor in patients with ASS. A reticular pattern on CT scan correlates with persistent fibrosis and destruction of pulmonary architecture, and it is not affected by treatment.¹³

Acute interstitial pneumonia, DLCO <45% and unusual interstitial pneumonia on CT scan are also related to poor prognosis.^{4 10}

A high level of suspicion is necessary to make an early diagnosis and avoid the irreversible changes in lung architecture that determine a persistent respiratory incapacity, worse prognosis and deterioration of functional status.

Learning points

- ▶ Consider inflammatory myositis when proximal muscle weakness is present.
- ▶ Consider antisynthetase syndrome when lungs and muscles are involved.
- ▶ A high level of suspicion is necessary to make an early diagnosis and start appropriate treatment before irreversible damage takes place.
- ▶ There is no strong evidence for treatment choice. Therefore, in severe cases an aggressive treatment, combining cyclophosphamide and glucocorticoids as used in systemic vasculitis, is suggested.

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Competing interests None.

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REFERENCES

- 1 Fischer A, Swigris JJ, du Bois RM, *et al.* Anti-synthetase syndrome in ANA and anti-Jo-1 negative patients presenting with idiopathic interstitial pneumonia. *Respir Med* 2009;103:1719–24.
- 2 Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. *Curr Rheumatol Rep* 2011;13:175–81.
- 3 Saketkoo LA, Ascherman DP, Cottin V, *et al.* Interstitial lung disease in idiopathic inflammatory myopathy. *Curr Rheumatol Rev* 2010;6:108–19.
- 4 Marie I, Josse S, Decaux O, *et al.* Clinical manifestations and outcome of anti-PL7 positive patients with antisynthetase syndrome. *Eur J Intern Med* 2013;24:474–9.
- 5 Connors GR, Christopher-Stine L, Oddis CV, *et al.* Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest* 2010;138:1464–74.
- 6 Labirua-Iturburu A, Selva-O'Callaghan A, Vincze M, *et al.* Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature. *Medicine (Baltimore)* 2012;91:206–11.
- 7 Yamasaki Y, Yamada H, Nozaki T, *et al.* Unusually high frequency of autoantibodies to PL-7 associated with milder muscle disease in Japanese patients with polymyositis/dermatomyositis. *Arthritis Rheum* 2006;54:2004–9.
- 8 Koenig M, Fritzler MJ, Targoff IN, *et al.* Heterogeneity of autoantibodies in 100 patients with autoimmune myositis: insights into clinical features and outcomes. *Arthritis Res Ther* 2007;9:R78.

- 9 Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. *Curr Opin Rheumatol* 2010;22:633–8.
- 10 Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. *Curr Opin Rheumatol* 2005;17:701–6.
- 11 Mercer LK, Moore TL, Chinoy H, *et al*. Quantitative nailfold video capillaroscopy in patients with idiopathic inflammatory myopathy. *Rheumatology (Oxford)* 2010;49:1699–705.
- 12 Selva-O'Callaghan A, Fonollosa-Pla V, Trallero-Araguás E, *et al*. Nailfold capillary microscopy in adults with inflammatory myopathy. *Semin Arthritis Rheum* 2010;39:398–404.
- 13 Schnabel A, Reuter M, Biederer J, *et al*. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. *Semin Arthritis Rheum* 2003;32:273–84.

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