CASE REPORT

Ro-positive interstitial lung disease treated with cyclophosphamide

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SUMMARY

Interstitial lung disease (ILD) comprises a spectrum of conditions involving inflammation and/or fibrosis of the alveolar wall causing limitation in gaseous exchange. Treatment varies depending on the underlying ILD. We describe the case of a woman presenting with a productive cough who was diagnosed with community-acquired pneumonia. While on the ward she developed type-1 respiratory failure requiring continuous positive airway pressure and intensive care unit admission. Failing to respond to targeted antimicrobials she was investigated by chest high-resolution CT and autoantibody screen to identify non-infective causes of her respiratory signs and symptoms. These demonstrated diffuse ground-glass change with peripheral honeycombing in keeping with fibrosis and alveolitis alongside high titres of anti-SS-A/Ro antibodies. She was managed with reducing course of steroids and immunosuppression with cyclophosphamide. The rationale of long-term immunosuppression was based on a presumed diagnosis of lung-dominant connective tissue disease, a disease concept proposed in contemporary medical literature.

BACKGROUND

Interstitial lung disease (ILD), synonymous with diffuse parenchymal lung disease, leads to

widespread inflammatory and/or fibrotic change in the lung parenchyma. Patients typically present with shortness of breath secondary to diminished gaseous exchange or dry cough. Classification of ILD can be challenging and the recent American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement on the classification of idiopathic interstitial pneumonias gives guidance on the most appropriate investigation to facilitate specific diagnosis.¹ These include high-resolution CT (HRCT) with surgical biopsy if features are atypical clinically or from HRCT.

The presence of circulating autoantibodies is thought to raise the possibility of a connective tissue disease (CTD) associated ILD.² For such patients the first or only significant manifestation of their CTD are respiratory symptoms due to ILD. A new disease concept, the lung-dominant CTD (LD-CTD) has been suggesting as a diagnosis for such patients^{3,4} also referred to in the literature as IPAF (interstitial pneumonia with autoimmune features⁵).

Here, we present a case of a patient presenting with respiratory symptoms of cough and progressive respiratory failure who had circulating anti-SS-A/Ro antibodies and radiographic features of both non-specific interstitial pneumonia and organising pneumonia (NSIP/OP).

CASE PRESENTATION

A 71-year-old, female, ex-smoker presented with a productive cough and was diagnosed with community-acquired pneumonia. Initial plain chest radiographs identified diffuse inflammatory changes, more confluent at the left base (figure 1). After developing type-1 respiratory failure, she was sent to intensive care unit where she required ventilation and continuous positive airway pressure. As she improved, she underwent tracheostomy tube placement; this remained in situ for 1 month. Infection was treated initially with meropenem and clarithromycin but then covered with tigecycline and vancomycin for 2 weeks. In spite of targeted antimicrobials, the productive cough persisted along with progression of pulmonary consolidation on chest radiography, thus HRCT imaging of the chest and an autoantibody screen was performed to identify other potential causes.

INVESTIGATIONS

HRCT demonstrated multifocal mediastinal lymphadenopathy, extensive ground-glass lung changes,

Figure 1 Plain film chest imaging demonstrating diffuse inflammatory changes. Initial radiograph demonstrates widespread patchy inflammatory markings with a predominant peripheral distribution more confluent at the left base.

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Figure 2 High-resolution CT chest imaging demonstrating features of non-specific interstitial pneumonia (NSIP) and organising pneumonia. Axial images at the level of the apex (A), carina (B) and bases (C) demonstrating diffuse ground-glass change (red) at all levels alongside interlobular septal thickening (green) characteristic of NSIP. More focal consolidation can be appreciated in a predominantly subpleural and peripheral distribution (blue) more characteristic of organising pneumonia. Traction bronchial dilatation may also be appreciated (yellow).

evidence of interlobular septal thickening and honeycomb fibrotic changes suggesting NSIP (figure 2A–C). More focal peripheral consolidation suggested an additional organising pneumonia component (figure 2C). These features led to a diagnosis of NSIP/OP.

Following treatment with intravenous hydrocortisone and reducing course of prednisolone a repeat HRCT study was performed to assess disease response. This demonstrated a significant improvement in the degree of lymphadenopathy and extent of ground-glass change (figure 3A,B) as well as the development of some basal traction bronchial dilatation reflecting established fibrosis.

Inpatient spirometry was performed demonstrating a predominantly restrictive pattern with a maintained FEV1/FVC (forced

Figure 3 High-resolution CT chest imaging demonstrating significant radiological response to steroid therapy. Coronal HRCT before (A) and after (B) steroid therapy and showing significant improvement of ground-glass appearance with residual honeycomb change and traction bronchial dilatation reflecting established fibrosis (yellow).

expiratory volume in 1 s/forced vital capacity) ratio of 0.82 and a reduced gas transfer of 63%.

Autoantibody screen was found to be positive for nuclear antibodies. Further investigation demonstrated a positive extractable nuclear antigens (ENAs) screen with anti-SS-A/Ro antibodies >240 ELIA kU/L.

TREATMENT

The patient was managed with reducing course of steroids and targeted antimicrobials as for an exacerbation of ILD. The presence of anti-SS-A/Ro antibodies in this patient raised the suspicion of LD-CTD, which rationalised the use of immunosuppression with cyclophosphamide.

OUTCOME AND FOLLOW-UP

This patient will be followed up in rheumatology outpatients department to monitor recovery and progress of her ILD and response to cyclophosphamide.

DISCUSSION

HRCT findings were of NSIP/OP that can be seen with a variety of aetiological agents. As such, a radiological diagnosis does not define the underlying cause of this ILD nor guide appropriate management. To this end, formal ILD classification is required. The ATS/ERS consensus,¹ which sets out the most contemporary scheme for the classification of ILD, would label this case as unclassified idiopathic interstitial pneumonia on the basis of organising pneumonia with supervening fibrosis. It suggests treatment to be solely a reducing regimen of steroids without

Box 1 Proposed criteria by Fischer *et al*⁴ for LD-CTD. Reproduced with permissions of the copyright owner

- ▶ NSIP, UIP, LIP, OP and DAD (or DIP if no smoking history) as determined by surgical biopsy specimen or suggested by HRCT
- and
- ▶ Insufficient extrathoracic features of a definite CTD to allow a specific CTD designation
- and
- ▶ No identifiable alternative aetiology for IP
- and
- ▶ Any one of the following autoantibodies:
 - High-titre ANA (>1:320) or RF (>60 IU/mL)
 - Nucleolar ANA
 - Anti-CCP
 - Anti-Scl-70
 - Anti-Ro
 - Anti-La
 - Anti-dsDNA
 - Anti-Smith
 - Anti-RNA
 - Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, and others)
 - Anti-PM-Scl
 - Anticentromere
- or
- ▶ Histopathological features
 - Lymphoid aggregates with germinal centres
 - Extensive pleuritis
 - Prominent plasmacytic infiltration
 - Dense perivascular collagen

Note: ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CTD, connective tissue disease; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; HRCT, high-resolution CT; IP, interstitial pneumonia; LD-CTD, lung-dominant CTD; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; RF, rheumatoid factor; RNP, ribonucleoprotein; tRNA, transfer RNA; UIP, usual interstitial pneumonia.

recognising a role for non-steroidal immunosuppressive therapy. Extensive delays in diagnosing and instigating appropriate treatment for our patient likely led to the development of progressive respiratory failure.

The presence of positive ENA screen and anti-SS-A/Ro antibodies in this patient presenting with respiratory symptoms refractory to treatment for infection did raise the possibility of a LD-CTD. Previous reports have demonstrated improvement in anti-SS-A/Ro-positive ILD in response to immunosuppressants with cyclophosphamide allowing tapering of corticosteroids.⁶ It has been proposed that up to 15% of patients diagnosed with ILD have underlying CTD⁷ and also that patients with ILD and circulating autoantibodies without extrathoracic features of rheumatological disease can be labelled as having LD-CTD using diagnostic criteria outlined in box 1. Such criteria would justify the use of the LD-CTD label and thus rationalise the use of immunosuppression with cyclophosphamide in our patient to potentiate the effects of steroids. Furthermore, it suggests the

importance of monitoring of the patient for evolving signs and symptoms of more formal CTDs.⁸

It is thought that the presence of autoantibodies may precede the diagnosis of CTDs, including systemic lupus erythematosus (SLE) by many years. A study which looked at the serum of 30 patients who went on to be diagnosed with SLE found the presence of anti-SS-A/Ro antibodies prior to diagnosis in 48% with a mean latency between the presence of antibodies and diagnosis of greater than 3.8 years.⁹

This case illustrates the complexity of classifying an individual case of ILD and determining the underlying aetiology. It also reflects the importance of the input of a multidisciplinary team to facilitate diagnosis and guide management.

Learning points

- ▶ Interstitial lung disease (ILD) should be investigated for features of autoimmunity.
- ▶ ILD with features of autoimmunity without features of a definitive connective tissue disease (CTD) can be diagnosed as lung dominant CTD (LD-CTD).
- ▶ LD-CTD can be treated with steroid sparing agents.

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