



CASE REPORT

Organising pneumonia can be the inaugural manifestation in connective tissue diseases, including Sjögren's syndrome

A.C. Henriët*, E. Diot^{#,*†}, S. Marchand-Adam^{*†}, A. de Muret[†], O. Favelle[§],
B. Crestani^{†,***} and P. Diot^{*†}

ABSTRACT: Connective tissue diseases are known to be one of the causes of organising pneumonia (OP). However, this association is rare and signs of OP usually occur in the context of an already diagnosed disease. We report three cases of OP preceding the articular symptoms of the underlying connective tissue disease by 3–6 months in two cases of rheumatoid arthritis and by 36 months in one patient with primary Sjögren's syndrome. The diagnosis of post-infectious OP had initially been suspected in the three cases and the patients had not been followed up further. The occurrence of OP preceding articular or any other extrapulmonary involvement of connective tissue disease had been reported in only four cases in the literature and, to our knowledge, no case preceding Sjögren's syndrome had ever been reported. These observations suggest that exhaustive investigations should be considered when OP is diagnosed, including antinuclear auto-antibodies and investigations for Sjögren's syndrome, even when there are no clinical signs suggesting an underlying connective tissue disease. These investigations should also be repeated during the course of the disease, especially in the case of OP continuing to progress under treatment and, of course, if signs of connective tissue disease appear.

KEYWORDS: Connective tissue disease, organising pneumonia, Sjögren's syndrome

Connective tissue disease is known to be one of the causes of organising pneumonia (OP). However, this association is rare and signs of OP usually occur in the context of an already diagnosed disease. We report three cases of OP presenting clinical features suggesting an infectious origin, and which proved to be the inaugural signs of rheumatoid arthritis (two cases) and Sjögren's syndrome (one case), highlighting the need for immunological follow-up in cases of OP.

CASE ONE

A 69-yr-old female was admitted with a clinical and radiological presentation of right upper-lobe pneumonia. She was a nonsmoker and had no significant past medical history. After 23 days of antibiotics the clinical situation remained unchanged and a computed tomography (CT) scan revealed bilateral alveolar densities, predominantly on the right side, associated with mediastinal lymph nodes, and a localised pleural effusion in the right apex. Bronchoscopy did not detect any abnormality and no infectious agent was found. A surgical

lung biopsy was performed on the right lower lobe which exhibited endoluminal obstruction of distal airspaces by fibrous granulation tissue, consistent with the diagnosis of OP. 1 mg·kg⁻¹ prednisone treatment was begun, with dramatic improvement allowing the dose to be tapered off. 8 months later, when the prednisone dose had been tapered down to 10 mg·day⁻¹ with no respiratory symptoms, the patient complained of diffuse arthralgia. Rheumatoid factor (RF) was positive, as was anti-cyclic citrullinated peptide antibody (titre 5.9 for a positivity threshold of 1 by immunoenzymatic technique). Rheumatoid arthritis was diagnosed. Despite the increase of prednisone up to 20 mg·day⁻¹, a chest radiograph revealed the development of bilateral alveolar opacities. Methotrexate was then associated to prednisone, resulting in clinical and radiological improvement.

CASE TWO

A 33-yr-old female who had never smoked and with no significant past medical history presented with clinical and radiological signs of

AFFILIATIONS

*Service de pneumologie et explorations fonctionnelles respiratoires,
#Service de médecine interne B,
†Service d'anatomie pathologique,
§Groupement d'imagerie médicale, CHRU de Tours,
†Unité INSERM U618, Faculté de médecine, Université François Rabelais, Tours,
†Service de Pneumologie, APHP, Hôpital Bichat-Claude-Bernard, and
***Unité INSERM U700, Faculté de X. Bichat, Université René Descartes, Paris, France.

CORRESPONDENCE

P. Diot
Service de pneumologie et explorations fonctionnelles respiratoires
CHRU de Tours
2 boulevard Tonnelé
37044 Tours cedex
France
E-mail: diot@med.univ-tours.fr

Received:
March 09 2010
Accepted after revision:
March 16 2010

PROVENANCE

Submitted article, peer reviewed.

right lower lobe pneumonia. Antibiotics produced no radiological improvement, and the patient lost 6 kg over 10 weeks. A chest CT was then performed and revealed alveolar opacities of the right lower lobe. There was a biological inflammatory syndrome and RF was positive. Bronchoalveolar lavage (BAL) revealed a mixed alveolitis (cell count $450,000 \text{ mL}^{-1}$; neutrophils 38%, macrophages 27%, lymphocytes 27% and eosinophils 8%). Transbronchial biopsies revealed OP characterised by intra-alveolar buds of granulation tissue and chronic inflammation in the surrounding alveoli. The evolution was marked by signs of diffuse arthritis with no radiological articular abnormalities. Anti-cyclic citrullinated peptide antibody was positive at $468 \text{ U}\cdot\text{mL}^{-1}$ (normal values $<25 \text{ U}\cdot\text{mL}^{-1}$ by ELISA technique). The patient was diagnosed with rheumatoid arthritis and treated with $40 \text{ mg}\cdot\text{day}^{-1}$ prednisone. Arthritis and respiratory signs disappeared and the chest radiograph normalised, allowing the steroid dose to be tapered off. When the dose was $6 \text{ mg}\cdot\text{day}^{-1}$, arthralgia recurred and hydroxychloroquine was added, with a good response.

CASE THREE

A 69-yr-old male nonsmoker with no significant past medical history presented clinical features suggesting severe bilateral infectious pneumonia. Chest radiography and a CT scan revealed consolidation with air bronchograms and ground-glass opacities in both lungs, associated with nodular opacities. Laboratory tests, including anti-Sjögren's syndrome A (anti-SSA), were negative. BAL revealed mixed alveolitis (cell count $1,100,000 \text{ mL}^{-1}$; neutrophils 21%, macrophages 38%, lymphocytes 38% and eosinophils 3%). Transbronchial biopsies revealed foci of alveolitis associated with plugs of fibrous tissue in distal bronchioles. OP was diagnosed and $60 \text{ mg}\cdot\text{day}^{-1}$ prednisone was prescribed with a tapering scheme. Although there was a dramatic response to the treatment, the OP relapsed twice, the first time when the patient was receiving $20 \text{ mg}\cdot\text{day}^{-1}$ prednisone (2 months into treatment), and the second time when the dose was $5 \text{ mg}\cdot\text{day}^{-1}$ (12 months into treatment). Prednisone dose was increased both times with a good response. There were no extrathoracic signs. Follow-up CT scans 9 months, 12 months and 26 months after onset revealed a decrease in parenchymal and ground-glass opacities, but also the development of fibrotic lesions with peripheral retraction, bilateral bronchiectasis and honeycombing in both lower lobes. Total lung capacity was 74% of the reference value at 9 months, and 42% at 12 months. At 26 months, the patient presented with inflammatory oedema of both hands and complained of xerostomia and xerophthalmia, which were confirmed by Schirmer and rose Bengal tests and by parotid scintigraphy. Minor salivary gland biopsy revealed a Chisholm grade I lymphocytic infiltration and anti-SSA antibodies were positive. Sjögren's syndrome was diagnosed. Despite the association of cyclophosphamide with the steroids, the patient deteriorated and eventually died from the evolution of pulmonary fibrosis 8 yrs after the onset of OP.

DISCUSSION

The concept of OP was introduced in the 2002 consensus statement of the American Thoracic Society and the European Respiratory Society for the classification of idiopathic interstitial pneumonia [1], to distinguish cryptogenic OP from cases

associated with various clinical conditions related to infections, drugs, radiotherapy and connective tissue disease [2].

The emergence of OP in the context of connective tissue disease is considered to be a poor prognosis factor [3]. Among connective tissue diseases, OP has been reported mostly in rheumatoid arthritis, less frequently in secondary Sjögren's syndrome, rarely in primary Sjögren's syndrome (PSS) and systemic lupus erythematosus, and exceptionally in systemic sclerosis [4].

In most cases of OP related to rheumatoid arthritis, RF has been found to be positive at the onset of OP. Moreover, a markedly high titre of RF has been observed at onset or during the course of OP, with increased levels of disease activity parameters [3] associated with progression of OP, as in our second case. The occurrence of a high titre of RF is considered to be a risk factor for OP [2].

In PSS, pulmonary manifestations are observed in up to 75% of cases, in the form of nonspecific pneumonitis, usual interstitial pneumonitis and lymphocytic interstitial pneumonitis [5]. OP has been reported in only a few cases, during the course of known PSS in five cases, and concurrent with PSS in two other cases [3, 6].

The occurrence of OP preceding articular or any other extrapulmonary involvement of connective tissue disease has been reported in only four cases to date [3], and, to our knowledge, no case preceding Sjögren's syndrome has ever been reported [7].

In our patients, the OP preceded the articular symptoms of the underlying connective tissue disease by 3–6 months in the two cases of rheumatoid arthritis and by 36 months for the patient with PSS. In case one, the occurrence of articular manifestations 6 months after the diagnosis of OP led to the identification of RF and anti-cyclic citrullinated peptide antibody, and to the diagnosis of rheumatoid arthritis. In case two, RF was assayed and found at a high level after 12 weeks of poor outcome under antibiotics. The diagnosis of rheumatoid arthritis was fully established 3 months later following arthralgia of multiple joints with a simultaneous increase in the RF titre and positivity of anti-cyclic citrullinated peptide antibody. In case three, the patient had no symptoms of PSS, and the laboratory tests, including antinuclear antibodies and RF, were negative when the OP diagnosis was made. PSS symptoms began 32 months later, and only then was the diagnosis established, based on the criteria proposed by the American–European Consensus Group [8]. PSS may in fact present with moderate or nonspecific initial symptomatology, which may lead to an under-diagnosis and, therefore, an underestimation of the possible link between OP and underlying but undiagnosed PSS [6, 7]. This case is also atypical in that sense that the bad evolution and the changes in the imaging suggest that OP may have been complicated by another form of pulmonary involvement, such as usual interstitial pneumonitis [9].

Overall, these observations suggest that exhaustive investigations should be considered when OP is diagnosed, including antinuclear auto-antibodies, RF, anti-cyclic citrullinated peptide antibody and investigations for Sjögren's syndrome, even

when there are no clinical signs suggesting an underlying connective tissue disease. These investigations should also be repeated during the course of the disease, especially in the case of OP continuing to progress under treatment and, of course, if signs of connective tissue disease appear. It is clearly important to link the OP to its related disease, as this may influence the prognosis [10] and, therefore, management. In most cases, there is a good response to corticosteroids at a dose of 0.75 to 1 mg·kg⁻¹ per day. However, in some cases there is little or no improvement. In these cases, cytotoxic drugs, such as azathioprine or cyclophosphamide, may be considered [2].

STATEMENT OF INTEREST

None declared.

REFERENCES

- 1 American Thoracic Society/European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277–304.
- 2 Cordier JF. Cryptogenic organizing pneumonia. *Eur Respir J* 2006; 28: 422–446.
- 3 Mori S, Cho I, Koga Y, *et al.* A simultaneous onset of organizing pneumonia and rheumatoid arthritis, along with a review of the literature. *Mod Rheumatol* 2008; 18: 60–66.
- 4 Sara AG, Hamdan AJ, Hanaa B, *et al.* Bronchiolitis obliterans organizing pneumonia: pathogenesis, clinical features, imaging and therapy review. *Ann Thorac Med* 2008; 3: 67–75.
- 5 Parambil JG, Myers JL, Lindell RM, *et al.* Interstitial lung disease in primary Sjögren syndrome. *Chest* 2006; 130: 1489–1495.
- 6 Lambert M, Hebban M, Viget N, *et al.* Bronchiolitis obliterans with organized pneumonia: a rare complication of primary Gougerot–Sjögren syndrome. *Rev Med Interne* 2000; 21: 74–77.
- 7 Ioannou S, Toya SF, Tomos P, *et al.* Cryptogenic organizing pneumonia associated with primary Sjögren's syndrome. *Rheumatol Int* 2008; 28: 1053–1055.
- 8 Vitali C, Bombardieri S, Jonsson R, *et al.* European Study Group on Classification Criteria for Sjögren's Syndrome. Classification for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. *Ann Rheum Dis* 2002; 61: 554–558.
- 9 Antoniou K, Margaritopoulos G, Economidou F, *et al.* Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement. *Eur Respir J* 2009; 33: 882–896.
- 10 Alasaly K, Muller N, Ostrow DN, *et al.* Cryptogenic organizing pneumonia. A report of 25 cases and a review of the literature. *Medicine (Baltimore)* 1995; 74: 201–211.