CASE REPORT

Migratory pulmonary infiltrates in a patient with rheumatoid arthritis

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Thorax 2002;**57**:465–467

The case history is described of an elderly man with rheumatoid arthritis receiving treatment with sulfasalazine and the cyclooxygenase-2 inhibitor celecoxib who presented with severe shortness of breath, cough, and decreased exercise tolerance. The chest radiograph showed unilateral alveolo-interstitial infiltrates and a biopsy specimen of the lung parenchyma showed changes consistent with acute eosinophilic pneumonia. Antibiotic treatment was unsuccessful, but treatment with steroids and discontinuation of sulfasalazine and celecoxib resulted in a marked clinical improvement confirmed by arterial blood gas analysis. The condition may have developed as an adverse reaction either to sulfasalazine or to celecoxib, although hypersensitivity to the latter has not previously been reported.

CASE REPORT

A 78 year old man with rheumatoid arthritis and chronic airways obstruction presented with a 5 day history of severe shortness of breath, cough, and decreased exercise tolerance. There was no history of fever, chills, wheezing, haemoptysis, chest pain, loss of appetite or weight, smoking, recent travel, or contact with pets. Past medical history was notable for coronary artery disease, atrial fibrillation, and iron deficiency anaemia. The patient had been on sulfasalazine and hydroxy-chloroquine for the past 4 years and celecoxib for the past 4 months. Physical examination revealed an elderly man in marked respiratory distress with a respiratory rate of 36 breaths/min, an irregular pulse of 92 beats/min, and a blood

pressure of 150/70. Respiratory examination was significant for mid to late inspiratory crackles in the right inframammary region with good air entry. There was no lymphadenopathy, skin rash, jugular venous distension, clubbing, or pedal oedema. Swelling of the proximal interphalangeal joints consistent with rheumatoid arthritis was noted. Cardiovascular, abdominal, and neurological examination was unremarkable. Laboratory data on admission revealed a white cell count of $7.8 \times 10^9/l$ without eosinophilia, unremarkable liver and kidney function tests, and an erythrocyte sedimentation rate of >140 mm/h. Arterial blood gas analysis on admission revealed a pH of 7.47, P_{aO_2} of 7.5 kPa (56 mm Hg), P_{aCO_2} of 4.5 kPa (34 mm Hg), and oxygen saturation of 0.78 on oxygen given via nasal cannula at a rate of 2 l/min. The admission chest radiograph (fig 1) was consistent with an alveolo-interstitial infiltrate in the right lower lobe.

The patient was treated with amoxicillin/clavulanic acid with a partial subjective response. Over the next 2 weeks severe shortness of breath recurred. A repeat chest radiograph revealed a new alveolo-interstitial infiltrate in the right middle lobe with clearing of the right lower lobe (fig 2). Over the next few days new infiltrates appeared in the right upper lobe with partial clearing of the right middle lobe. The left lung remained radiologically clear.

A transbronchial biopsy was performed. The biopsy specimen consisted of multiple pieces of lung parenchyma, all showing the same changes. There was a large amount of fibrin present in the alveolar spaces and bronchiolar lumen (fig 3). The alveolar exudate had many eosinophils with fewer

Figure 1 Chest radiograph on admission (PA view) showing alveolar and interstitial infiltrates in the right lower lobe and evidence of prior cardiac surgery.

Figure 2 Chest radiograph 2 weeks later (PA view) showing alveolar and interstitial infiltrates in the right middle lobe with clearing of the right lower lobe infiltrate. The left lung fields remain radiologically clear.

Figure 3 Transbronchial biopsy specimen of the lung parenchyma with intra-alveolar fibrinous exudate showing early organisation; the alveolar septa are widened due to inflammatory cells and fibroblasts. Magnification $\times 220$.

Figure 4 Enlarged view of the alveolar content and interstitium showing many eosinophils (arrows) in both the fibrinous exudate and the interstitium. Images of the eosinophils have been computer enhanced for better visibility. Magnification $\times 440$.

Figure 5 Chest radiograph (PA view) 2 weeks after treatment with steroids showing complete radiological resolution of the right lung infiltrates.

Box 1 Proposed diagnostic criteria for acute eosinophilic pneumonia⁶

- Acute febrile illness (days, rarely weeks, duration).
- Hypoxaemic respiratory failure.
- Diffuse alveolar/mixed alveolar interstitial radiographic changes.
- BAL eosinophils $>25\%$ or biopsy confirmation of eosinophilic lung infiltrates.*
- No identifiable infection.
- Prompt and complete response to steroids.
- Failure to relapse after discontinuation of steroids.

*Biopsy evidence of acute and/or organising diffuse alveolar damage with eosinophils is the most characteristic feature, but marked tissue eosinophilic infiltrate with clinical confirmation of the history is also sufficient.

neutrophils and mononuclear cells, and showed evidence of early organisation (fig 4). The interstitial space showed widening due to a mixture of oedema, inflammatory cells similar to those in the alveoli, and organisation. Many airspaces showed hyperplasia of type II pneumocytes. Hyaline membranes were absent, as was bronchiolar organisation. There was no evidence of vasculitis or embolisation. Stains for bacteria, mycobacteria, and fungi were negative for microorganisms. Foci of squamous metaplasia were seen in the bronchioles. The pathological changes were indicative of acute eosinophilic pneumonia.

Treatment with steroids and discontinuation of sulfasalazine and celecoxib resulted in a marked clinical improvement in the patient confirmed by arterial blood gas analysis on room air which gave a pH of 7.47, P_{aO_2} 11.5 kPa (86 mm Hg), P_{aCO_2} 4.7 kPa (35 mm Hg). A repeat chest radiograph showed complete resolution of the infiltrates (fig 5).

On subsequent follow up over 2.5 years the patient has been free of respiratory symptoms since sulfasalazine and celecoxib were discontinued and the 2 week course of prednisone was instituted.

DISCUSSION

Migratory pulmonary infiltrates are recognised in many lung diseases, the prototype of which is Loeffler's syndrome. Other causes include lupus pneumonitis,¹ cocaine smoking,² bronchiolitis obliterans with organising pneumonia, radiation pneumonitis, vasculitic syndromes including Wegener's granulomatosis, and many of the pulmonary eosinophilic syndromes. Causes of pulmonary eosinophilia include allergic bronchopulmonary mycoses, parasitic infestations, drug reactions, eosinophilia-myalgia syndrome, Loeffler's syndrome, chronic eosinophilic pneumonia, allergic granulomatosis of Churg and Strauss, hypereosinophilic syndrome, and acute eosinophilic pneumonia.³

Acute eosinophilic pneumonia is a recently described illness^{4,5} that appears to be clinically distinct from the well recognised entity of chronic eosinophilic pneumonia. It is characterised by acute respiratory insufficiency, hypoxaemia, diffuse radiographic infiltrates, and eosinophilia on lung biopsy specimens in the absence of infection, atopy, or asthma.⁶ A rapid response to steroids with resolution of symptoms and a relapse free course are characteristic of the disease. Pathological findings include diffuse alveolar damage with eosinophilic infiltrates in the pulmonary interstitium and alveoli. The diagnostic criteria for acute eosinophilic pneumonia proposed by Tazelaar *et al*⁶ are shown in box 1.

The pathological differential diagnosis includes classic diffuse alveolar damage, chronic eosinophilic pneumonia, Loeffler's syndrome, infections, and allergic reactions. Unlike

cases of diffuse alveolar damage, acute eosinophilic pneumonia responds promptly to steroid treatment and has a uniformly good prognosis. It is therefore important to differentiate cases of acute eosinophilic pneumonia from diffuse alveolar damage. Furthermore, acute eosinophilic pneumonia is distinguished from classic diffuse alveolar damage by the presence of conspicuous tissue eosinophils, a finding not seen in the usual form of diffuse alveolar damage⁷ or acute interstitial pneumonia.⁸ In addition, cases of acute eosinophilic pneumonia described in the past have cited diffuse pulmonary involvement⁹ and the radiological picture is often indistinguishable from pulmonary oedema. Our patient was unusual in that the radiological abnormalities were confined to the right hemithorax. To our knowledge, unilateral presentation of acute eosinophilic pneumonia has not previously been described.

The cause of acute eosinophilic pneumonia remains unknown. It has been suggested that this syndrome may result from an acute hypersensitivity phenomenon to an inhaled antigen⁵ or it may be related to a factor yet unknown. In our patient it may well represent drug hypersensitivity.

Though rare, pulmonary toxicity has been associated with sulfasalazine which is independent of the duration or dose of the drug.⁷ Reported pathological lesions include chronic eosinophilic pneumonia, chronic interstitial pneumonia, desquamative interstitial pneumonia, bronchiolitis obliterans with organising pneumonia, and diffuse alveolar damage.⁷ However, there is only one case report¹⁰ which describes sulfasalazine induced lung disease which may be classified as acute eosinophilic pneumonia according to the diagnostic criteria proposed by Tazelaar *et al* (box 1). In this case, as in ours, the patient's presentation was acute in onset with cough and hypoxaemia. However, whereas our case had been on sulfasalazine for the preceding 4 years, in the previously reported case sulfasalazine had been introduced only 3 weeks before the onset of symptoms. Furthermore, in the case reported previously the patient had bilateral pulmonary infiltrates whereas our patient had unilateral infiltrates. To our knowledge, unilateral presentation of acute eosinophilic pneumonia has not previously been described. Both patients responded very well to steroids and had a relapse free course after steroids were withdrawn.

In the patient presented here hypersensitivity to celecoxib is also possible, although an extensive review of the literature did not reveal any known pulmonary toxicity to the drug. Cyclooxygenase (COX), an essential enzyme in the pathway of prostaglandin formation from arachidonic acid, exists in two isoforms: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is expressed under normal physiological conditions whereas COX-2, the inducible isoform, is associated with inflammation. Celecoxib is a selective inhibitor of COX-2, and there is accumulating evidence that the induction and regulation of COX-2 may be key elements in the pathophysiological process of a number of inflammatory disorders and may play an important role in the pathogenesis of pulmonary

inflammation.¹¹ At the same time, COX-2 induction may also lead to potentially beneficial results such as enhanced production of anti-inflammatory and bronchoprotective substances such as prostaglandin E2. The consequences of COX-2 expression and its inhibition in the lung are therefore likely to be complex and depend on the balance between the pro-inflammatory and anti-inflammatory effects of prostanoids produced by various cell types under different circumstances. In a recently conducted trial to evaluate the effect of the COX-2 inhibitor celecoxib on bronchial responsiveness and cough reflex sensitivity in patients with asthma, it was concluded that a 7 day course of the maximal approved dose of celecoxib did not significantly affect pulmonary function, bronchial responsiveness, or cough reflexivity.¹²

Ethical considerations precluded a re-challenge of our patient with either sulfasalazine or celecoxib to confirm drug related hypersensitivity. The patient continues to be treated with hydroxychloroquine for rheumatoid arthritis and remains symptom free.

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Revised version received 29 August 2001

Accepted for publication 19 September 2001

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