Migratory pulmonary infiltrates in a patient with rheumatoid arthritis

S Mehandru, R L Smith, G S Sidhu, N Cassai, C P Aranda

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 hydroxychloroquine 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 $7.8 \times 10^3/l$ without eosinophilia, unremarkable liver and kidney function tests, and an erythrocyte sedimentation rate of $>140 \text{mm/h}$. Arterial blood gas analysis on admission revealed a pH of 7.47, PaO$_2$ of 7.5 kPa (56 mm Hg), PaCO$_2$ 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
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, PaO₂ 11.5 kPa (86 mm Hg), PaCO₂ 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 illness4,5 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 al6 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

<table>
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<tr>
<th>Box 1 Proposed diagnostic criteria for acute eosinophilic pneumonia</th>
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<tr>
<td>• Acute febrile illness (days, rarely weeks, duration).</td>
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<td>• Hypoxaemic respiratory failure.</td>
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<td>• Diffuse alveolar/mixed alveolar interstitial radiographic changes.</td>
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<td>• BAL eosinophils &gt;25% or biopsy confirmation of eosinophilic lung infiltrates.*</td>
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<td>• No identifiable infection.</td>
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<td>• Prompt and complete response to steroids.</td>
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<td>• Failure to relapse after discontinuation of steroids.</td>
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<td>*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.</td>
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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 ×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 ×440.

Figure 5 Chest radiograph (PA view) 2 weeks after treatment with steroids showing complete radiological resolution of the right lung infiltrates.
cases of diffuse alveolar damage, acute eosinophilic pneumo-
nia responds promptly to steroid treatment and has a
uniformly good prognosis. It is therefore important to
differentiate cases of acute eosinophilic pneumonia from diff-
use alveolar damage. Furthermore, acute eosinophilic pneu-
monia 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 damage or acute
interstitial pneumonia. In addition, cases of acute eosino-
philic pneumonia described in the past have cited diffuse
pulmonary involvement 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 presen-
tation 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 antigen 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 sulphasalazine which is independent of the duration or dose of
the drug. Reported pathological lesions include chronic eosino-
philic pneumonia, chronic interstitial pneumonia, desqua-
mative interstitial pneumonia, bronchiolitis obliterans with
organising pneumonia, and diffuse alveolar damage. However,
there is only one case report which describes sulphasalazine induced lung disease which may be classified as
acute eosinophilic pneumonia according to the diagnostic cri-
teria 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
sulphasalazine for the preceding 4 years, in the previously
reported case sulphasalazine had been introduced only 3 weeks
before the onset of symptoms. Furthermore, in the case
reported previously the patient had bilateral pulmonary inflit-
irates 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 condi-
tions whereas COX-2, the inducible isform, 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 pathophys-
iological process of a number of inflammatory disorders and
may play an important role in the pathogenesis of pulmonary
inflammation. At the same time, COX-2 induction may also
lead to potentially beneficial results such as enhanced produc-
tion of anti-inflammatory and bronchoprotective substances
such as prostaglandin E2. The consequences of COX-2 expres-
sion 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 relexivity.

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 re-
 mains symptom free.

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