LESSON OF THE MONTH

Recurrent lung shadowing in adult juvenile idiopathic arthritis

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Case report

A 25 year old Asian woman with a 11 year history of juvenile idiopathic arthritis (polyarthritis, rheumatoid factor positive) was referred from a peripheral hospital with poor disease control despite multiple disease modifying anti-rheumatic drugs (DMARDs). She was not a cigarette smoker and had been taking azathioprine 125 mg daily and prednisolone 5 mg daily for the past 10 months. Her past medical history included pulmonary tuberculosis diagnosed 14 months ago for which she had completed six months of antituberculous treatment. Details of her previous respiratory management including radiographs were not available. Physical examination revealed generalised synovitis with normal respiratory findings. She was treated with intra-articular corticosteroid injections into multiple joints and sulfasalazine was added to her above medications. Sulfasalazine was increased to a dose of 2 g daily over a four week period.

One month later, she re-presented with about two weeks history of dry cough and dyspnoea. Physical examination revealed that she was afebrile with normal respiratory findings and persistent synovitis. Based on her chest radiograph (fig 1A) showing patchy consolidation in the right lung, more prominently in the right mid and upper zones, and left lower zone, the presumed diagnosis was pneumonia, possibly with an atypical microorganism and she was treated with a course of ampicillin and erythromycin while investigations were performed. The main differential diagnosis was the recurrence of pulmonary tuberculosis. Laboratory investigations were largely unchanged from the previous month, with a normochromic normocytic anaemia of 9.0 g/dl and mild leucocytosis of $12.2 \times 10^9/l$, although she had now developed an eosinophilia of $3.54 \times 10^9/l$ ($0.04-0.44 \times 10^9/l$). Her electrolytes were normal, C reactive protein was 185, antinuclear antibody, antineutrophilic cytoplasmic antibody and cryoglobulins were negative. Serum electrophoresis showed an acute phase response. Investigations for faecal parasites were found to be negative. Despite the antibiotics, a repeat chest radiograph one week later (fig 1B) demonstrated more extensive consolidation in the right lung affecting predominantly the mid and lower zones. The consolidation in the left lung was also more prominent. A diagnosis of

drug induced eosinophilic pneumonia was now considered with sulfasalazine being the most likely cause. Sulfasalazine was stopped and she was given prednisolone 40 mg daily (reducing dose). On review two weeks later, she had symptomatically improved and a repeat chest radiograph (fig 1C) was normal. Her eosinophil count had returned to normal value of 0.14 within five days of withdrawing sulfasalazine.

This patient's notes and results of investigations were subsequently obtained from the referring hospital. She had been given sulfasalazine 15 months ago and was on a dose of 2 g daily when she was admitted four weeks after starting sulfasalazine because of poor disease control. Although she did not have any respiratory symptoms at that time, her chest radiograph (fig 2A) was abnormal, demonstrating consolidation in the left upper zone radiating from the hilum. Bronchial washings were negative for acid fast bacilli but given her degree of immunosuppression and recent trip to Pakistan it was decided to treat her for tuberculosis with rifampicin, isoniazid and pyrazinamide. Two weeks later she complained of increasing breathlessness and her chest radiograph demonstrated progressive consolidation in the left lung. She was started with a reducing dose of prednisolone and her symptoms improved. Her chest radiograph at this stage (fig 2B), showed clearing of the left upper zone, but extensive consolidation in the left mid and lower zones. There was also some evidence of consolidation in the right lower zone. Three weeks after cessation of her prednisolone, her breathlessness and dry cough recurred. Laboratory tests revealed a marked eosinophilia of $4.24 \times 10^9/l$ and her chest radiograph showed extensive right lung abnormalities (fig 2C). The sulfasalazine was withdrawn and she improved clinically. Her chest radiograph subsequently returned to normal.

Discussion

Sulfasalazine is commonly used for the treatment of rheumatoid arthritis. Adverse events such as nausea, vomiting, rashes, fever, headache, blood dyscrasias and hepatic dysfunction are common, but lung complications from sulfasalazine administration are rare.^{1 2} Most cases of sulfasalazine induced lung complications have been reported in patients with

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Figure 1 Serial posteroanterior chest radiographs. (A) One month after commencement of sulfasalazine when she presented with a dry cough and dyspnoea, showing patchy consolidation right lung, left apex and lower zone. (B) One week later, after the course of antibiotics with more extensive consolidation. (C) Two weeks after discontinuation of sulfasalazine treatment showing a normal chest radiograph.

inflammatory bowel disease. Eosinophilic pneumonitis is the most common reported respiratory complication, although fibrosing alveolitis and tracheo-laryngitis with bronchospasm have been described.¹ A MEDLINE database search revealed only three reported cases of sulfasalazine related pulmonary complications in rheumatoid arthritis patients.³⁻⁵ Only one of these cases had eosinophilic pneumonitis, the other being sub-acute hypersensitivity pneumonitis without evidence of

Figure 2 Serial posteroanterior chest radiographs from 1997. (A) One month after introduction of sulfasalazine demonstrating consolidation left upper zone with peripheral patches of consolidation right middle and left lower zones. A clinical diagnosis of pulmonary tuberculosis was made at this time. (B) While on a tapering dose of prednisolone, with clearing of left upper zone and some consolidation in left and right lower zones. (C) Three weeks after discontinuation of prednisolone demonstrating extensive consolidation right lung.

peripheral eosinophilia, and the third, fibrosing alveolitis. In our patient, the diagnosis of sulfasalazine induced eosinophilic pneumonitis was based on her clinical findings, marked blood eosinophilia and chest radiograph appearances. Furthermore, an inadvertent re-challenge to sulfasalazine caused a return of symptoms, eosinophilia and pulmonary

Table 1 Drugs that can cause eosinophilic pulmonary reactions

<i>Cytotoxic</i>	<i>Antirheumatic</i>
Methotrexate	Gold
Bleomycin	Penicillamine
Procarbazine	<i>Anticonvulsant</i>
<i>Antibiotics</i>	Nitrofurantoin
Sulphonamides	Carbamazepine
Penicillins	Phenytoin
Tetracyclines	<i>Others</i>
	Sulfasalazine
	Ranitidine
	Nebulised pentamidine

infiltrates, which resolved after cessation of the drug and treatment with corticosteroids.

The clinical picture of eosinophilic pneumonitis is characterised by cough, fever, dyspnoea, and bilateral lung infiltrates and peripheral eosinophilia. The aetiology of eosinophilic pneumonitis is unclear, although hypersensitivity is almost certainly a factor. The radiological findings can vary widely and can mimic other conditions as shown by our patient who was treated as pulmonary tuberculosis initially. The most characteristic radiological features however are dense pulmonary infiltrations with ill defined margins at the periphery of both lungs.⁶ The pulmonary infiltrates may be migratory, as evident in this patient's chest radiographs in 1997. The radiological pattern of sulfasalazine induced eosinophilic pneumonitis is unlike that of gold or methotrexate associated hypersensitivity pneumonitis, whereby the most common pattern is that of diffuse interstitial infiltrates.⁷ Other processes, in particular infection or pulmonary involvement of rheumatoid arthritis need to be excluded. Some of the drugs that can cause eosinophilic pulmonary reactions are listed in

table 1.⁸ An important differential diagnosis is bronchiolitis obliterans organising pneumonitis, which may have similar radiological features and can occur in patients with arthritis, but is not associated with a peripheral eosinophilia. Treatment of eosinophilic pneumonitis consists of withdrawal of the drug and in severe cases, administration of corticosteroids.

The lesson

- Sulfasalazine is a commonly used drug and although hypersensitivity to sulfasalazine is rare, it should be considered in patients taking sulfasalazine who present with symptoms and radiological evidence of pulmonary disease.
- The overall prognosis of eosinophilic pneumonitis condition is generally good after withdrawal of the drug, although fatalities have been reported.⁹

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