Case Reports

Sulphasalazine-induced sub-acute hyper-sensitivity pneumonitis

J. Kolbe*†, D. Caughey‡ and S. Rainer§

Departments of *Respiratory Medicine and §Pathology, Green Lane Hospital, Auckland, and
Departments of †Medicine and ‡Rheumatology, Auckland Hospital, Auckland, New Zealand

Introduction

Sulphasalazine has been widely used for the treatment of inflammatory bowel disease for almost 50 yr and in the last decade has been increasingly used for the treatment of rheumatological conditions. It is a combination of 5-aminosalicylic acid (ASA) and sulphapyridine linked by a diazo bond. Adverse reactions are many, common and lead to discontinuation of therapy in 20–30% of patients. More serious side effects such as leukopenia, haemolytic anaemia and deranged hepatic function are less common while drug-induced pulmonopathy is rare (1). Pulmonary complications may be confused with manifestations of the underlying disease while the management and prognosis may be very different.

We report a patient who developed an unusual form of drug-induced pulmonopathy 17 months after starting sulphasalazine for a rheumatological condition not associated with pulmonary complications.

Case Report

A 67-year-old woman complained of recurrent arthritis in her first meta-tarsophalangeal joints for 20 yr before commencing allopurinol for presumed gout in 1975. In 1987 she developed pain and swelling of both wrists and several distal interphalangeal joints. Radiographs showed chondrocalcinosis in both wrists and knees consistent with calcium pyrophosphate deposition disease. Allopurinol was stopped and she was commenced on diclofenac sodium. In July 1988, because of persistent joint pain and scaling of the elbows and scalp, a presumptive diagnosis of psoriatic arthritis was made. Tests for rheumatoid factor and antinuclear antibodies were negative. Enteric-coated sulphasalazine was begun at a dose of 0.5 g daily, progressing to 1.0 g twice daily, which produced considerable improvement in joint symptoms. Two dermatologists subsequently felt that the diagnosis was astute tic eczema rather than psoriasis. In November 1989 she developed paroxysmal non-productive cough and dyspnoea on mild exertion.

Hypertension had been well controlled on cyclopenthiazide 0.5 mg daily and pindolol 15 mg twice a day for 15 yr and these drugs were continued. She had a 35 pack per year smoking history but had not smoked for 20 yr. She had no exposure to dusts, fumes, chemicals or specific organic antigens. There was no previous history of drug allergy.

On examination she was afebrile and on auscultation medium inspiratory bilateral basal crackles to the mid-chest were heard. There was no finger clubbing, lymph-adenopathy, hepatosplenomegaly nor ocular abnormality.

Investigations showed a haemoglobin of 122 g L⁻¹ white blood count 8.5 × 10⁹ L⁻¹ with 86% neutrophils, 9% lymphocytes, no eosinophils and an ESR of 39 mm h⁻¹. Electrolytes, liver function tests, uric acid and thyroid function tests were all normal. Arterial blood gas on air results were pH = 7.49, PCO₂ = 34 mmHg (4.5 kPa), PO₂ = 70 mmHg (9.3 kPa), bicarbonate = 26 mmol L⁻¹ and an oxygen saturation of 95%. Chest radiograph [Plate 1(a)] revealed bilateral basal alveolar and interstitial opacities. Serum precipitins, rheumatoid factor, tissue auto-antibodies and viral and chlamydia antibody titres were all negative. Pulmonary function tests showed a restrictive pattern, impaired CO transfer and desaturation on exercise. Bronchoscopy revealed a normal tracheobronchial tree. Histology of transbronchial lung biopsies showed a range of changes, predominantly in the alveolar walls. The majority of alveolar walls were normal. Some were thickened by mature fibrous tissue and some contained an infiltrate of histiocytes and lymphocytes. In areas, these histiocytes had an epithelioid appearance and multinucleated giant cells were seen.
Isolated Masson bodies were present. The appearances were those of sub-acute hyper-sensitivity pneumonitis (Plate 2).

Sulphasalazine was stopped and because of a lack of improvement over days she was commenced on prednisone 30 mg daily. Serial chest radiographs and
pulmonary lung function tests showed improvement over the following months. She returned symptomatically, radiologically [Plate 1(b)] and physiologically to normal after 6 months. Prednisone was gradually discontinued over a total of 6 months. At more than a year after steroid cessation there has been no further deterioration in symptoms or pulmonary function. Re-challenge was not undertaken.

Discussion

Pulmonary complications of sulphasalazine therapy are rare. Most reported cases of drug-induced pulmonopathy due to sulphasalazine in which pulmonary histology was available may be classified as an eosinophilic pneumonitis (2–10). Diffuse interstitial fibrosis (fibrosing alveolitis) (11–15) and obliterative bronchiolitis have also been reported (6,8). This is the first report of sub-acute hyper-sensitivity pneumonitis in association with sulphasalazine. Raforth (16) reported the case of a young woman who developed systemic non-caseating granulomata 3 weeks after starting sulphasalazine for Crohn's disease. However, non-caseating granulomata are well recognized in non-digestive tissue in Crohn's disease, reflecting its multi-system nature. Occasional granulomata were noted in the case reported by Williams et al. (6), although the major histological abnormalities were of bronchiolitis obliterans and fibrosing alveolitis.

Most cases of sulphasalazine-induced pulmonopathy have been reported in patients receiving the drug for inflammatory bowel disease. In the English literature there are only two other cases of sulphasalazine-induced lung disease reported in patients taking the drug for other than inflammatory bowel disease (17,18). Both patients had rheumatoid arthritis. No pulmonary histology was presented in one, whilst in the other the pattern was that of fibrosing alveolitis - also, the type of diffuse interstitial lung disease associated with rheumatoid disease. The development of bilateral pleural effusions in the case reported by Geborek et al. (17) would be most unusual for drug-induced pulmonopathy and thus raises the possibility that both the effusions and lung parenchymal disease were complications of the rheumatoid arthritis. Despite the temporal relationship with sulphasalazine administration, the case described by Boyd et al. (18) may represent 'rheumatoid lung' responding to oral corticosteroids.

The patient described in this report had a rheumatological condition not associated with pulmonary complications. Whilst a definite aetiologic role for
sulphasalazine cannot be proven in the absence of rechallenge, it is likely that sulphasalazine was the etiologic agent in this case because of the temporal relationship between drug introduction and the development of symptoms, the lack of other medical conditions or exposures which may have been responsible for interstitial lung disease and the lack of recurrence of disease following withdrawal of oral cortico-steroids.

This patient did not improve following cessation of the drug and oral cortico-steroids were required for symptomatic improvement and for restoration of pulmonary function to normal. This feature is well recognized in other drug-induced pulmonopathies, particularly those forms other than acute eosinophilic pneumonitis (19). Perhaps once the immunological mechanism is underway, drug withdrawal alone is insufficient to reverse it.

Which component of the drug and the mechanism of action responsible for the type of pulmonopathy seen in this case are unknown. In cases of sulphasalazine-induced alveolitis, the sulphapyridine component has been thought responsible because when this moiety was replaced re-challenge occurred without adverse effect. Also, eosinophilic pneumonitis has been reported in association with sulphonamide use (20). Aspirin has been implicated as the causative agent in eosinophilic pneumonitis (21) and non-cardiogenic pulmonary oedema (22). It is uncertain as to whether these complications may also be associated with 5-amino-salicylic acid. The type of inflammation in this present case suggests a type of delayed hyper-sensitivity reaction to a component of the drug. Non-caseating granulomata in the liver and lymph nodes have been reported in association with drug hypersensitivity, including to the sulphonamides (23).

Hence, sulphasalazine must be considered as a potential cause of diffuse lung disease in patients taking the drug for rheumatological conditions as well as inflammatory bowel disease. This case illustrates that sulphasalazine may be associated with sub-acute hypersensitivity pneumonitis, as well as previously recognized forms of drug-induced lung disease. Clinical, radiological or physiological features cannot reliably distinguish the various histological forms of sulphasalazine-induced pulmonopathy and a definitive histological diagnosis is essential.

References


