Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement

P.C. Wong, W.W. Yew, C.F. Wong, H.Y. Choi

ABSTRACT: A 67 year old woman presented with miliary tuberculosis. She was treated with streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide. However, she developed rifampicin-induced thrombocytopenia after 6 weeks of treatment, and skin rash, blood eosinophilia and pulmonary infiltrates after 8 weeks of therapy. The latter was found to be ethambutol related. Additional evidence, including blood and sputum eosinophilia and the rapidity of its response to corticosteroid, suggested that the pulmonary infiltrates might also be eosinophilic in nature.

To the best of our knowledge, this constitutes the first report of such adverse drug reaction, induced by ethambutol.


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Eosinophilic alveolitis, as a form of hypersensitivity lung disease incurred by antimicrobial agents, has been well described [1]. Amongst the incriminated antimicrobial agents, sulphonamide and penicillin are the classically documented examples [2, 3]. Para-aminosalicylic acid and isoniazid are the two antituberculous drugs that have been reported to cause pulmonary eosinophilia [4–6]. Rifampicin has been reported to cause blood eosinophilia, but only in the presence of other drugs, such as isoniazid or streptomycin [7, 8]. We report a case of ethambutol-induced blood eosinophilia and pulmonary infiltrates probably also eosinophilic in nature, which to the best of our knowledge has not previously been documented in the literature.

Case report

A 67 year old housewife presented to our unit with fever of unknown origin. Her chest radiograph showed diffuse small nodular opacities (fig. 1). She was diagnosed to be suffering from miliary tuberculosis, and was treated with streptomycin 0.75 gm i.m. 5 days-week⁻¹, together with isoniazid 300 mg q.d., rifampicin 450 mg q.d., ethambutol 800 mg q.d. and pyrazinamide 1.5 gm q.d. by the oral route. Fever subsided promptly in 2 weeks after commencement of this drug regimen. Mycobacterium tuberculosis infection was later confirmed by positive sputum and urine culture. The organism was sensitive to the five drugs administered, as well as to ofloxacin.

In spite of lack of history of allergy to drugs, thrombocytopenia was noted after 6 weeks of in-patient supervised treatment with the five drug antituberculous regimen. The platelet count dropped from $277 \times 10^9 \cdot l^{-1}$ on admission to $49 \times 10^9 \cdot l^{-1}$. It promptly returned to $175 \times 10^9 \cdot l^{-1}$ after cessation of rifampicin for 4 days.

After a further 3 days the patient developed an itchy maculopapular skin eruption. Haematological examination revealed blood eosinophilia. The absolute blood eosinophil count rose from $0.19 \times 10^9 \cdot l^{-1}$, on admission to $2.24 \times 10^9 \cdot l^{-1}$. Streptomycin-induced eosinophilia was suspected [9], and for this reason the drug was stopped. Ofloxacin, 400 mg q.d. per os, was added.
was only 85% when breathing room air. The patient required supplemental oxygen at 4 L·min⁻¹ by nasal prongs to raise the \( \text{Sao}_2 \) to 98%. Her absolute blood eosinophil count was \( 1.95 \times 10^9 \) cells·L⁻¹ on that occasion. Sputum showed a moderate amount of eosinophils. All antituberculosis drugs were stopped. Prednisolone, 30 mg q.d., was administered orally following the clinical diagnosis of severe drug reaction causing the lung infiltrate skin rash and eosinophilia. After two doses of prednisolone, the absolute blood eosinophil count decreased to \( 0.19 \times 10^9 \) cells·L⁻¹. A chest radiograph also showed significant improvement (fig. 3). Arterial hypoxaemia resolved completely after 1 week of steroid therapy, and the \( \text{Sao}_2 \) return to 98% when breathing room air. Marked radiographic clearing of the lung was noted after 2 weeks of steroid therapy (fig. 4). Sputum eosinophils were no longer found by the third week of steroid therapy.

Three weeks later, whilst the patient was still on prednisolone, 30 mg q.d., ofloxacin and ethambutol at the same dosages as utilized previously were recommenced. Unfortunately, there was prompt recrudescence of skin rash and blood eosinophilia after one dose of these two drugs. The blood absolute eosinophil count rose from \( 0.24 \times 10^9 \) L⁻¹ to \( 0.90 \times 10^9 \) cells·L⁻¹. However, chest radiograph showed no deterioration. The rash and blood eosinophilia resolved over 5 days following the cessation of ofloxacin and ethambutol. One week later, the patient was successfully put back on isoniazid and ofloxacin. Pyrazinamide was added another 2 weeks later, after ascertaining that she could tolerate the former two drugs. Her cutaneous reaction and peripheral blood eosinophilia did not recur, and she was given prednisolone treatment for a total of 12 weeks with gradual reduction of dosage. A chest radiograph taken 2 weeks after cessation of steroid treatment was found to show quite clear lung fields (fig. 5). The patient was finally discharged home and continued to receive isoniazid, ofloxacin and
Discussion

This patient had rather severe drug reactions with two antituberculous agents. Rifampin administration led to thrombocytopenia and ethambutol to skin rash, eosinophilia and pulmonary infiltrates. The first reaction has been well documented in the literature, though said to be more commonly associated with intermittent administration of the drug [10–12]. Ethambutol-related haematological reaction has rarely been reported, and usually in the form of neutropenia or thrombocytopenia [13, 14]. We recently reported an isolated case of concomitant neutropenia and eosinophilia due to ethambutol [15].

In this patient, the development of eosinophilia and skin rash after stopping rifampin was initially thought to be due to streptomycin, a drug commonly causing these adverse reactions. The patient, however, deteriorated with pulmonary involvement clinically and radiologically, together with persistence of the eosinophilia and skin rash, despite discontinuation of streptomycin. Ethambutol was later found to induce the dermatological and haematological reaction. Isoniazid, pyrazinamide and ofloxacin were then successfully reintroduced, and the patient remained well.

The exact pathological finding of the pulmonary reaction induced by ethambutol, unfortunately, cannot be ascertained. Fibreoptic bronchoscopy with transbronchial biopsy and bronchoalveolar lavage were not performed, because the patient was critically ill with gross arterial oxygen desaturation at that time. The clinical impression of a drug-induced pulmonary reaction did not warrant an open lung biopsy. We suspect that it probably represents a form of pulmonary eosinophilia, because of the concomitant blood and sputum eosinophilia, the acuteness of its onset, and the dramatic response to corticosteroid [16, 17].

The list of agents implicated in eosinophilia and drug-induced pulmonary disease is ever-expanding. We would like to propose, subject to further experience, that ethambutol should be considered a possible agent in causing eosinophilia and drug-induced pulmonary reaction, perhaps also eosinophilic in nature.

References