Eur Respir J, 1995, 8, 866–868
DOI: 10.1183/09031936.95.08050866
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

CASE REPORT

Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement

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

Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. P.C. Wong, W.W. Yew, C.F. Wong, H.Y. Choi. ©ERS Journals Ltd, 1995.

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.

Eur Respir J., 1995, 8, 866–868.

Tuberculosis and Chest Unit, Grantham Hospital, Hong Kong.

Correspondence: P.C. Wong
Tuberculosis and Chest Unit
Grantham Hospital
125 Wong Chuk Hong Road
Hong Kong

Keywords: Blood, eosinophilia, ethambutol, lung

Received: May 31 1994
Accepted after revision November 26 1994

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-aminosalicyclic 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 $277\times10^9\cdot l^{-1}$ on admission to $49\times10^9\cdot l^{-1}$. It promptly returned to $175\times10^9\cdot l^{-1}$ 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 0.19×10^9 cells·l^{-1}, on admission to 2.24×10^9 cells·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

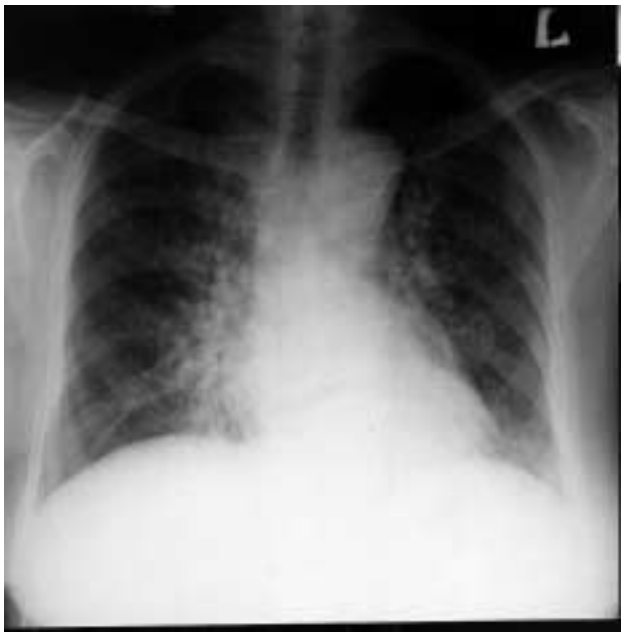

Fig. 1. – Chest radiograph on presentation; showing diffuse mottlings of both lungs highly suggestive of miliary tuberculosis.

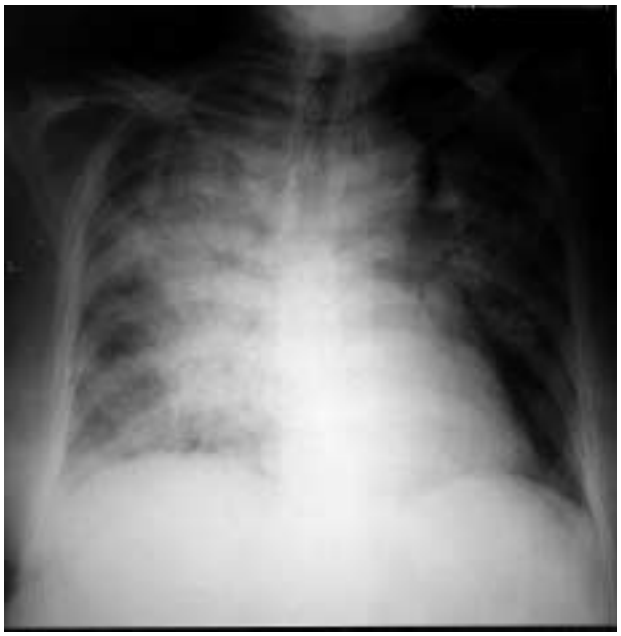

Fig. 2. – Chest radiograph taken when the patient experienced dyspnoea and had eosinophilia; showing bilateral dense perihilar infiltrates together with nodular peripheral infiltrates.

to constitute a regimen that consisted of ofloxacin, isoniazid, ethambutol and pyrazinamide. However, the patient's cutaneous reaction and the eosinophilia did not improve over the next 7 days.

Eight weeks after initiation of antituberculosis treatment, the patient started to develop fever and acute dyspnoea. Her chest radiograph showed marked deterioration in terms of development of bilateral confluent air-space consolidation in the perihilar regions and nodular shadowing in the more peripheral regions (fig. 2). Measurement of blood gases showed arterial hypoxaemia with hypocarbia. Arterial oxygen saturation (Sa,o_2) was only 85% when breathing room air. The patient required supplemental oxygen at 4 $L \cdot min^{-1}$ by nasal prongs to raise the Sao_2 to 98%. Her absolute blood eosinophil count was 1.95×10^9 cells$\cdot L^{-1}$ 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 0.19×10^9 cells$\cdot L^{-1}$. A chest radiograph also showed significant improvement (fig. 3). Arterial hypoxaemia resolved completely after 1 week of steroid therapy, and the 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 $0.24 \times 10^9 \cdot L^{-1}$ to 0.90×10^9 cells$\cdot L^{-1}$. 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

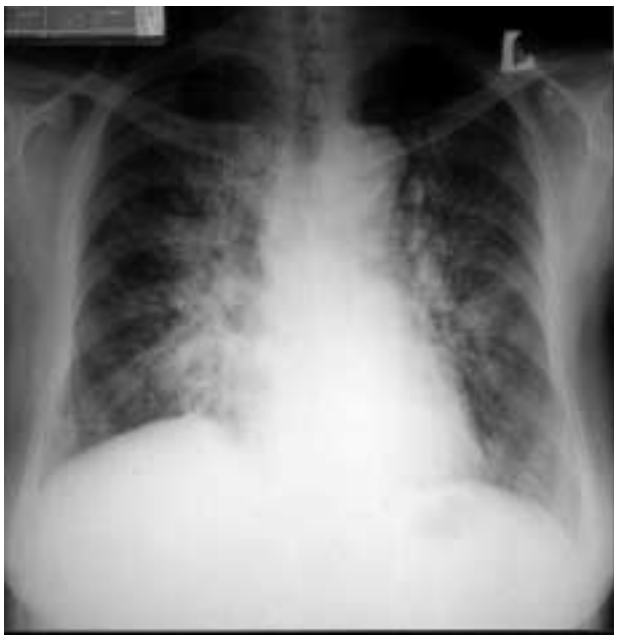

Fig. 3. – Chest radiograph taken after 2 doses of 30 mg prednisolone; showing significant clearing of shadows as compared to figure 2.

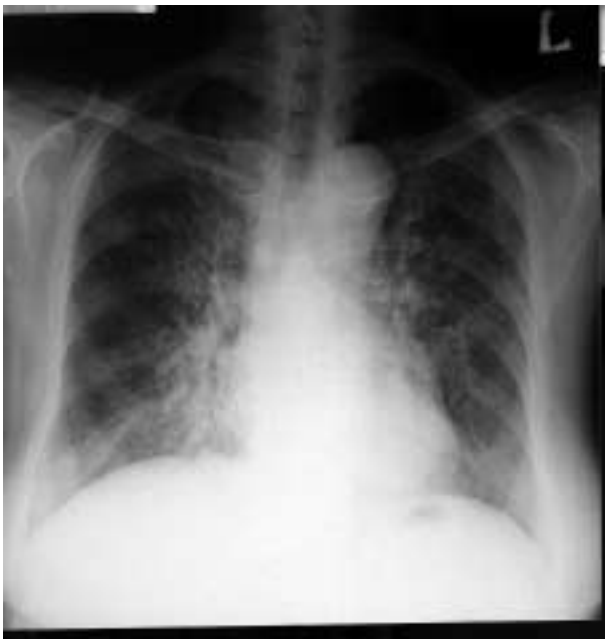

Fig. 4. – Chest radiograph taken after 2 weeks of steroid therapy; showing almost complete clearing of shadows.

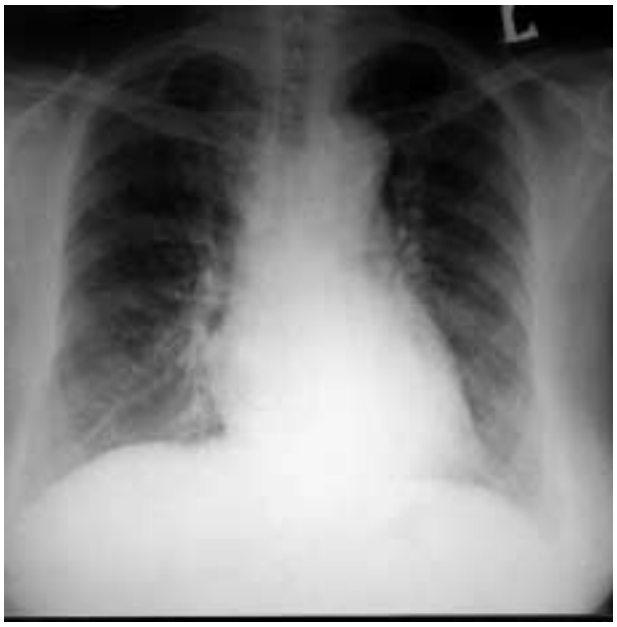

Fig. 5. – Chest radiograph taken 2 weeks after stopping steroid treatment; showing no recurrence of pulmonary infiltrates.

pyrazinamide on an out-patient basis. Reassessment, 2 months after withdrawal of steroid, revealed no recurrence of eosinophilia, and the chest radiograph remained clear.

Discussion

This patient had rather severe drug reactions with two antituberculous agents. Rifampicin 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 rifampicin 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

1. Cooper JAD, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2. Noncytotoxic drugs. *Am Rev Respir Dis* 1986; 133: 488–505.
2. Fiegenberg DS, Weiss H, Kirshman H. Migratory pneumonia with eosinophilia associated with sulfonamide administration. *Arch Intern Med* 1967; 120: 85–89.
3. Reichlin S, Loveless MH, Kane EG. Loeffler's syndrome following penicillin therapy. *Ann Intern Med* 1953; 38: 113–120.
4. Warring FC, Howlett KS. Allergic reaction to para-aminosalicyclic acid. *Am Rev Tuberc* 1952; 65: 235–249.
5. Wold DE, Zahn DW. Allergic (Loeffler's) pneumonitis occurring during antituberculous chemotherapy: report of three cases. *Am Rev Tuberc* 1956; 74: 445–453.
6. Demeter SL, Ahmad M, Tomashefski JF. Drug-induced pulmonary disease. I. Patterns of response. *Cleve Clin Q* 1979; 46: 89–99.
7. Mungall IPF, Standing VF. Eosinophilia caused by rifampicin. *Chest* 1978; 74: 321–322.
8. Lee M, Berger HW. Eosinophilia caused by rifampicin. *Chest* 1980; 77: 579.
9. Wykoff RF. Eosinophilia. *South Med J* 1986; 79: 608–612.
10. Blajchman MA, Lowry RC, Pettit JE, Stradling P. Rifampicin-induced immune thrombocytopenia. *Br Med J* 1970; 3: 24–26.
11. Esposito R, Vitali D. Rifampicin and thrombocytopenia. *Lancet* 1971; ii: 491–492.
12. Hadfield JW. Rifampicin-induced thrombocytopenia. *Postgrad Med J* 1980; 56; 59–60.
13. Holdiness MR. A review of blood dyscrasias induced by the antituberculosis drugs. *Tubercle* 1987; 68: 301–309.
14. Rabinovitz M, Pitlik SD, Halevy J, Rosenfield JB. Ethambutol-induced thrombocytopenia. *Chest* 1982; 81: 765–766.
15. Wong CF, Yew WW. Ethambutol-induced neutropenia and eosinophilia. *Chest*, 1994; 106: 1638–1639.
16. Carrington CB, Addington WW, Goff AM, *et al*. Chronic eosinophilic pneumonia. *N Engl J Med* 1969; 280: 787–798.
17. Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia: a report of 19 cases and a review of the literature. *Medicine* 1988; 67: 154–162.