

## CASE REPORT

## Pneumonitis induced by rifampicin

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An 81 year old man was admitted to hospital with pulmonary *Mycobacterium tuberculosis* infection and was treated with rifampicin (RFP), isoniazid (INH), and ethambutol (EB). On day 9 he developed fever and dyspnoea. Chest radiographs showed new infiltration shadows in the right lung. Bronchoalveolar lavage (BAL) was performed and increased numbers of lymphocytes were recovered. Drug induced pneumonitis was suspected so the antituberculous regimen was discontinued and methylprednisolone was administered. The symptoms and infiltration shadows improved. INH and EB were reintroduced without any recurrence of the abnormal shadows. T cell subsets in the BAL fluid and a positive lymphocyte stimulation test for RFP suggest that RFP induced pneumonitis may be related to a complex immunological response.

Rifampicin (RFP) is an important drug in the treatment of tuberculosis and is used in multidrug regimens. Side effects from RFP are common and include hepatitis, fever, and blood disorders.<sup>1</sup> However, RFP induced pneumonitis is rare and we are aware of only one previously reported case.<sup>2</sup> We report a patient with a severe pulmonary infiltration probably resulting from a delayed type immune reaction to RFP.

## CASE REPORT

An 81 year old man was admitted to hospital with fever and a productive cough in February 1999. His past history was remarkable for pulmonary tuberculosis at the age of 35. On

physical examination his blood pressure was 146/96 mm Hg and the pulse rate was 82 beats/min. Coarse inspiratory crackles were noted over the left lung fields. Cardiac examination was normal and no lymph nodes were palpable. A chest radiograph revealed infiltrates in the left upper lung and a pleural effusion in the left lower lung (fig 1). The white blood cell (WBC) count was 6070/μl with 74.8% neutrophils, 19.1% lymphocytes, 5.1% monocytes, 0.7% eosinophils, and 0.3% basophils. C reactive protein (CRP) was 1.1 g/dl. Arterial blood gas analysis gave Pao<sub>2</sub> 8.5 kPa, Paco<sub>2</sub> 5.2 kPa, and pH 7.45. Acid-fast bacilli were detected in the sputum (Gaffky 2) and the culture yielded *Mycobacterium tuberculosis*.

Beginning on day 2, RFP (0.3 g/day), isoniazid (INH, 0.3 g/day), and ethambutol (EB, 0.5 g/day) were administered and the pleural effusion was drained. After administration of these drugs the symptoms diminished gradually. On day 9 the patient developed fever and dyspnoea. At this time a chest radiograph and CT scans showed new interstitial shadows in the right lung (fig 2). The WBC count increased to 13 540/μl with 81.0% neutrophils, 5.5% lymphocytes, 11.0% monocytes, and 2.5% eosinophils. The CRP concentration was 17.4 g/dl. Arterial blood gas analysis gave Pao<sub>2</sub> 9.5 kPa, Paco<sub>2</sub> 6.0 kPa, pH 7.39 (on nasal oxygen at a rate of 8 l/min). Bronchoalveolar lavage (BAL) was performed using 100 ml of a sterile saline solution (30% recovery). The BAL fluid contained 82.9% lymphocytes, 13.6% neutrophils, and 3.5% macrophages. The CD4/CD8 ratio of the BAL fluid lymphocytes was 10.5. A presumptive diagnosis of drug induced pneumonitis was made and the antituberculous regimen was stopped. Methylprednisolone (1000 mg/day) was administered for 3 days because of progressive respiratory failure. Prednisolone (50 mg/day)



**Figure 1** Chest radiograph on admission showing infiltrates in the left upper lung and a pleural effusion in the left lower lung.



**Figure 2** Chest radiograph on day 9 showing new interstitial shadows in the right lung.

was started on day 12. The symptoms and the diffuse interstitial shadows diminished gradually.

A drug lymphocyte stimulation test (DLST) was performed. The lymphocyte stimulation index by RFP was 370%, by INH was 170%, and by EB was 130%. We concluded that the pneumonitis was induced by RFP. The prednisolone dose was tapered slowly and the symptoms and diffuse interstitial shadows diminished gradually. Streptomycin (0.5 g/day) was administered on day 26. INH (0.3 g/day) and EB (0.5 g/day) were reintroduced after an interval of 3 months from the time of withdrawal. These agents were given for another 6 months without any recurrence of the abnormal shadows on the chest radiographs.

## DISCUSSION

Antituberculous agents are known to produce various adverse effects.<sup>1</sup> There have been some reported cases of pneumonitis and a systemic lupus erythematosus-like syndrome induced by INH.<sup>3</sup> However, RFP induced pneumonitis is very rare with only one reported case in the literature.<sup>2</sup>

In our patient a positive DLST for RFP and a successful challenge test with INH and EB support the presumptive diagnosis of RFP induced pneumonitis. The mechanism of drug induced pneumonitis has been reported to be either an immunological reaction or a cytotoxic effect.<sup>4,5</sup> The high DLST value for RFP suggests that the reaction in our patient might have been based on a delayed type immune reaction rather than a toxic effect. On the other hand, Umeki *et al* reported that the pulmonary fibrosis induced by RFP was probably due to a cytotoxic effect because of a negative DLST.<sup>2</sup> These apparently conflicting results suggest that RFP can induce pulmonary changes not only by an immunological mechanism but also by a cytotoxic effect.

The lymphocytes in the BAL fluid were significantly increased and this finding supports the diagnosis of drug induced pneumonitis associated with a pulmonary inflammatory response.<sup>6</sup> However, it differed from previous reports in that the CD4/CD8 ratio was increased. Drugs may also induce a change in the normal balance between helper and suppressor T cells in the lungs, which can give rise to inflammatory reactions. This can occur through the recognition of the drug itself as a foreign antigen, or by a change in the underlying immunological balance induced by the agent. It is reasonable to postulate from the increase in the total numbers of both the

helper and suppressor T cell subsets in the BAL fluid that drug induced pneumonitis represents a complex interaction of direct toxicity by the drug as well as an active immunological response.<sup>7</sup>

Life threatening respiratory distress related to chemotherapy, but not caused by drug hypersensitivity or toxicity, can occur in patients with pulmonary tuberculosis. An immunological reaction to the drug may be related to the pre-treatment immune status of the patient,<sup>8</sup> and this is the reason why the present case differs from previous reports in the mechanism of drug induced pneumonitis.<sup>2,6</sup>

Drug induced pneumonitis can be serious and even fatal unless the causative agents are promptly withdrawn. Although RFP induced pneumonitis is extremely rare, it is important to recognise that this antituberculous drug can cause such an adverse reaction.

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