

Brief communications

Pneumonitis and eosinophilia induced by ethambutol

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CASE REPORT

A 70-year-old Japanese man who did not smoke was admitted to the hospital on February 2, 1994, for treatment of right cervical tuberculous lymphadenitis, which was diagnosed on the basis of histologic changes showing caseation necrosis surrounded by Langhans' giant cells, epithelioid cells, and lymphocytes. He had no history of any exposure to drugs or chemicals. Except for the enlarged right cervical lymph nodes, ranging in size from 1 to 2 cm, results of physical examination and a chest x-ray study were both normal. The white blood cell count was $4.8 \times 10^9/L$ with $2.6 \times 10^9/L$ (54%) neutrophils and $0.10 \times 10^9/L$ (2%) eosinophils. Repeated sputum smears and cultures for acid-fast bacilli were negative. Results of an ELISA for HIV antibody were negative.

Treatment was initiated with a daily combination of isoniazid (400 mg), rifampicin (450 mg), and ethambutol (750 mg). The eosinophil count began to rise 7 days after initiation of therapy and reached a level of $0.70 \times 10^9/L$ on day 27. Liver function remained normal. On day 31, the patient became febrile ($38.5^\circ C$) with a nonproductive cough. At this time, a chest x-ray film showed diffuse bilateral reticulogranular infiltrates without pleural effusion. A bronchoalveolar lavage (BAL) and a transbronchial lung biopsy were performed. Leukocytes in the BAL consisted of 4% eosinophils, 76% macrophages, 13% neutrophils, and 7% lymphocytes. Cultures of the BAL specimen failed to reveal any pathogens. The biopsy specimens obtained from the right lower lobe (subsegment 8A) showed focal, mild alveolar thickening with a moderate infiltration of the alveoli and alveolar septa by histiocytes, lymphocytes, and eosinophils. There was no neutrophil infiltrate or granuloma formation.

We suspected a diagnosis of drug-induced pneumonitis and therefore discontinued the antituberculosis regimen 35 days after its initiation. On the next day, dry cough and fever disappeared. The chest x-ray film showed that lungs had cleared after 10 days, and the eosinophilia gradually resolved in 14 days.

In the lymphocyte stimulation test for antituberculosis drugs, ethambutol was the only agent to provide a positive result (Table I). The other two antituberculosis agents, isoniazid (400 mg/day) and rifampicin (450 mg/day), were reintroduced after an interval of 17 days and 25 days, respectively, from the time of their withdrawal. Administration of these agents was continued for another 6 months without recurrence of either the abnormal

Abbreviation used

BAL: Bronchoalveolar lavage

TABLE I. Lymphocyte stimulation test

Drug	Stimulation index (%)
Ethambutol	235
Rifampicin	81
Isoniazid	100

Stimulation index represents the ratio of the mean value of counts per minute of 1×10^6 cells in triplicate test vials divided by the mean value of counts per minute in triplicate control vials.

shadows on the chest x-ray films or eosinophilia. The patient ultimately recovered from the tuberculous lymphadenitis while on the two-drug regimen.

DISCUSSION

Ethambutol, a tuberculostatic agent that inhibits the transfer of mycolic acids to the cell wall, is a first-line drug for the curative treatment of tuberculosis.¹ It is generally well tolerated.¹ Its major adverse reactions include a dose-dependent form of retrobulbar neuritis that occurs in 1% or fewer of patients who received 15 mg/kg/day as a single oral dose.² Hypersensitivity reactions are infrequent and include dermatitis, arthralgias, and fever.²

The temporal relationship between the administration of ethambutol with pneumonitis and eosinophilia, together with the exclusively positive result of the lymphocyte stimulation test with this drug, provided evidence of a causal relationship. Although some patients with tuberculous infections may manifest pneumonitis or eosinophilia because of *Mycobacterium tuberculosis*, our patient did not have these manifestations before the start of antituberculosis therapy. Eosinophilia has been associated with ethambutol administration.³ However, there is no previous report of pneumonitis with eosinophilia caused by ethambutol. Our patient appears to be the first such case.

The proliferation and maturation of eosinophils are under the control of several lymphokines.⁴ Among these lymphokines, IL-5 is thought to be the most important and selective. In this case ethambutol may have caused the T cells to produce IL-5, leading to eosinophilia.⁴ The

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infiltration of eosinophils may cause tissue damage through secretory products from eosinophils such as cationic proteins, peroxidase, and neurotoxin.⁴ Because orally administered ethambutol is readily transferred into the lung tissue,⁵ the hyperreaction to ethambutol by T cells in the lung may have mobilized the eosinophils, leading to interstitial pneumonia.

Drug-induced pneumonitis can be serious and even fatal unless the causative agents are promptly withdrawn. Although ethambutol-induced pneumonitis appears to be rare, it is important to recognize that this antituberculosis drug can cause such an adverse reaction.

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A false-positive result with the American Society for Testing and Materials D5712-95 test method for protein given by a common vulcanization accelerator

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Type 1 allergic reactions to proteins present in natural rubber latex are well established and lead to the development of allergy in individuals exposed to inadequately leached rubber articles made from natural latex.¹ Users of all types of medical gloves therefore require assurance that the gloves they use have very low residual levels of water-extractable proteins, and suppliers need to be able to demonstrate that their gloves conform to this requirement.

The Food and Drug Administration (FDA) has established an upper limit of 50 µg of extractable protein per gram of glove (micrograms per gram) for gloves that are claimed to contain a low concentration of extractable protein. It has adopted the American Society for Testing and Materials (ASTM) D5712-95 test² as the method for determination of this concentration. The limit set is considered to be the limit of sensitivity for this method.³

METHODS

We have found that one commonly used vulcanization accelerator, 1,3-diphenylguanidine (DPG), provides a strong positive result with the ASTM test method. Thus by using a dispersing

Abbreviations used

ASTM:	American Society for Testing and Materials
DPG:	1,3-Diphenylguanidine
FDA:	Food and Drug Administration

agent (the sodium salt of a naphthalenesulfonic acid-formaldehyde condensation product), we prepared aqueous dispersions of various chemicals commonly used in compounding latex. The concentration of dispersing agent used varied from 2.6% to 9.8% of the aqueous phase, depending on the nature of the chemical being dispersed. All the milling and mixing equipment was thoroughly clean and had been rinsed three times with 5% aqueous sodium hydroxide to remove any traces of protein. Samples of the dispersions were centrifuged at 11,000 g for 1 hour to sediment the solid chemical, and the aqueous phases were then separated and analyzed for protein by the ASTM procedure.² Test solutions were recentrifuged if they were visibly turbid. The test procedure incorporates a method aimed at removing interfering substances by precipitation of the proteins followed by their redissolution in aqueous sodium hydroxide.² This method is mandatory and was followed rigorously. The results, expressed in terms of apparent protein concentration in parts per million, are shown in Table I.

RESULTS AND DISCUSSION

The aqueous phase of all the dispersions except the DPG dispersion produced results of less than 25 parts per million for apparent protein content. The DPG result was about 200 times greater and clearly represents a major

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