Endobronchial Tuberculosis Presenting As Asthma*

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Clinical deterioration with features suggestive of asthma was seen in three patients following two to six months of drug therapy of primary tuberculosis. There was a poor clinical response to administered bronchodilators. Bronchoscopy in all three revealed culture-negative mycobacterial caseating granulomas. Corticosteroid therapy resulted in good clinical response, with resolution of the asthmatic symptoms and improvement in the expiratory flow rates. In our opinion these patients are clinically compatible with a hypersensitivity response to mycobacteria following antituberculosis therapy and release of tuberculosis antigens. Corticosteroid therapy is appropriate in this form of tuberculous disease.

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An immunologic response to the tubercle bacilli has been recognized since its discovery. Following infection, resistance develops, and there is a decrease in the multiplication of bacilli in the macrophages. The majority of infected patients develop cell-mediated hypersensitivity to the tuberculin protein, which is reflected by the tuberculin dermal test. Normally, this delayed hypersensitivity is coupled to resistance to the tubercle bacilli; however, under some circumstances, the reaction may be detrimental.

The delayed hypersensitivity in response to the tubercle bacilli is not considered essential for immunity to develop. Hypersensitivity responses do represent maladaptation. While immunity and delayed hypersensitivity do coexist in tuberculosis, the two immune responses are extensions of each other.

We had three patients with primary pulmonary tuberculosis who received appropriate antituberculosis chemotherapy but had adverse clinical responses. They deteriorated clinically six to 26 weeks after chemotherapy, with the development of bronchial wheezing which was unresponsive to bronchodilators. Corticosteroid therapy produced a resolution of symptoms, and endobronchial granulomas were seen in all. This adverse clinical response to antituberculosis therapy responsive to corticosteroids is suggestive of an aberrant immunologic response.

CASE REPORTS

CASE 1

A seven-year-old caucasian boy was admitted with right middle lobe pneumonia and hilar lymphadenopathy. A tuberculin skin test done six months earlier was negative but converted to positive two weeks before admission. The diagnosis of Mycobacterium tuberculosi infection was confirmed by gastric lavage, and he was treated with isoniazid (INH), ethambutol, and streptomycin for two months. He was discharged home taking the INH and ethambutol, but readmitted one month later because of wheezing which was not relieved by theophylline. Spirometric study showed a forced vital capacity (FVC) of 0.89 L (49 percent of predicted) and a forced expiratory volume in one second (FEV1) of 0.75 L, demonstrating a restrictive defect which was associated with radiologically apparent atelectasis. Bronchoscopic and biopsy examination demonstrated an endobronchial granuloma of the right bronchus intermedius. Corticosteroids were administered with clinical and spirometric improvement. In three weeks he had a FVC of 1.71 L (85 percent of predicted) and FEV1 of 1.15 L. Follow-up bronchoscopy showed the granuloma to have completely disappeared.

CASE 2

A 15-month-old North American Native girl was admitted with pulmonary tuberculosis. A BCG vaccination had been given at birth, and her tuberculin skin test showed 15 mm of induration. A chest roentgenogram showed hilar lymphadenopathy and a right middle lobe infiltrate. Despite two months of appropriate antituberculosis chemotherapy (INH, rifampin, and streptomycin), she deteriorated clinically, with right upper and lower lobe consolidation. Bronchoscopic examination revealed a biopsy-proven granuloma with necrosis of the right main stem bronchus. Peripheral blood lymphocytes were normal quantitatively and functionally. The patient was removed from the hospital against medical advice by her mother soon after the bronchoscopy. She was discharged receiving INH and rifampin and was lost to follow-up.

CASE 3

A 25-year-old Cambodian male refugee who had immigrated to Canada in 1980 was admitted with confirmed pulmonary tuberculosis, and a chest roentgenogram showed a right upper lobe infiltrate with hilar lymphadenopathy. His tuberculin skin test had been negative previously but converted at the time of admission. Bronchoscopic evaluation performed before the initiation of therapy showed dysplastic changes in the right upper lobe orifice. Biopsy of this area showed metaplasia and mild inflammation with no evidence of tuberculosis. Isoniazid, rifampin, pyrazinamide, and capreomycin were given for six weeks before he was discharged taking INH and rifampin. Five months later he developed wheezing, aggravated by exercise and not relieved by inhaled theophylline and β-agonist inhalation. His admission spirometric examination showed a vital capacity of 4.51 L (60 percent predicted) and FEV1 of 2.51 L. A coaxial tomographic scan showed obstruction of his right upper lobe.

慌乱糊涂的抄袭

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FIGURE 1. Case 3. Coaxial tomogram of the chest before corticosteroid therapy showing right main stem bronchial mass with right upper lobe narrowing (closed arrows). Precarinal lymphadenopathy is present (open arrow).

which was confirmed on bronchoscopic study (Fig 1). Biopsy of this mass demonstrated caseating necrosis with no tubercle bacilli on culture or Ziehl-Nielsen staining. Bronchial lavage showed 65 percent macrophages, 17 percent lymphocytes, 3 percent polymorphonuclear leukocytes, and 14 percent unknown cells and epithelial cells. Bronchoscopic studies were repeated on two successive months and demonstrated gradual enlargement of the mass. The histologic features of the biopsies were those of a caseating granuloma with no evidence of tubercle bacilli. Prednisone, 25 mg daily, was given for four weeks, resulting in improvement of the wheezing. A repeated bronchoscopic examination showed a reduction in the size of the endobronchial mass. The right upper lobe bronchus could now be visualized. The histology of the mass after the corticosteroid therapy showed a granuloma with no caseation or tubercle bacilli. The patient continued receiving his antituberculosis therapy and four weeks of corticosteroid therapy.

DISCUSSION

Immune responses occur within 15 days following vaccination with tubercle bacilli and are characterized by the mobilization of lymphocytes and macrophages, which reduce and inhibit the growth of the bacilli. If hypersensitivity coexists, there is liquefaction and caseating necrosis, with an abundant growth of the tubercle bacilli and associated cavitation with clinical deterioration.

Endobronchial tuberculosis has been demonstrated in up to 18 percent of tuberculous patients. It arises from direct implantation of the tubercle bacilli into the bronchus or infiltration from the adjacent mediastinal lymph nodes. Tuberculous lymph node infiltration into the bronchus occurs mainly in children, while direct bronchial implantation is usually seen in cavitating tuberculosis. There has been a poor response of endobronchial tuberculosis to antituberculosis therapy, but it has not been documented as being associated with hypersensitivity.

These three patients had clinical features of primary tuberculosis with recent skin test conversion. All three patients deteriorated clinically and presented with wheezing that was found to be the result of a sterile endobronchial granuloma, despite appropriate antituberculosis therapy. This bronchoscopic demonstration of endobronchial tuberculous granulomas with negative cultures is similar to patients described by Ip and coworkers. Bronchoscopic examination on the third patient both before and after the development of the endobronchial granuloma demonstrated inflammation and metaplasia initially, and during the clinical deterioration there was histologic evidence of caseating necrosis with no tubercle bacilli. Coincident with corticosteroid therapy, there was a marked clinical improvement, with an associated bronchoscopic reduction in the size of the granuloma and a histologic absence of caseation. The histologic improvement suggests suppression of the hypersensitivity component of the immunologic reaction.

The clinical deterioration of these patients is unlikely to be due to the progression of the pulmonary tuberculosis. All had received appropriate antituberculosis therapy as judged by bacterial culture and antibiotic sensitivity. Patient 3 had six months of therapy before presenting with wheezing and deterioration. According to recommendations for short-course antituberculosis therapy, adequate treatment had been given. Sputum cultures as well as cultures of endobronchial biopsies were persistently negative in all of these patients.

The relief of airflow obstruction and wheezing occurring with resolution of the inflammation and caseation suggests suppression of hypersensitivity. We believe that the clinical response in these three patients resembles the Jarisch-Herxheimer reaction, which has been documented in the treatment of Treponema pallidum with penicillin. Our patients differed from those with the classic Jarisch-Herxheimer response in having a “delayed” hypersensitivity reaction following therapy, with culture-negative caseating granuloma, rather than an immediate reaction as seen in the therapy of T pallidum with penicillin. This delayed reaction is related to the slower destruction of the
mycobacteria by the antibacterial agent. We presume that the antituberculosis antibiotics killed the bacilli with release of tuberculoprotein causing a hypersensitivity reaction of inflammation, caseation and enlargement of the endobronchial tuberculomas. With suppression of the hypersensitivity response, there is clinical and histologic resolution.

The indications for corticosteroid therapy in tuberculosis are not completely defined. In our opinion, endobronchial tuberculomas under some circumstances represent a hypersensitivity response, which, if not rapidly responsive to conventional antituberculosis therapy, should be treated with corticosteroids. We recommend that tuberculous patients with wheezing have a bronchoscopic examination performed together with biopsies of the granuloma. Evidence of caseating necrosis with no tubercle bacilli suggests hypersensitivity appropriate for a trial of steroid therapy.

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