Bronchocentric Granulomatosis Associated with Rheumatoid Arthritis*

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A 49-year-old woman with biopsy-proved bronchocentric granulomatosis (BCG) had repeated exacerbations of seronegative rheumatoid arthritis and vasculitis of the skin concurrent with BCG. To our knowledge, there have been no prior reports of this form of systemic involvement in BCG. While its pathogenesis remains obscure, this case, along with another recent report of eye involvement, suggests that BCG is part of a widespread immunologic response and is not a distinct entity.

Bronchocentric granulomatosis (BCG) was described by Liebow in 1973.1 The clinical and radiologic patterns, as well as destructive granulomas, may resemble other pulmonary granulomatoses. However, the pattern of injury is to the bronchi and bronchioles, with only incidental involvement of adjacent vessels and no extrapulmonary involvement.1,2 Rheumatoid arthritis has infrequently been reported with BCG, and the existing reports do not relate the manifestations of BCG to the manifestations of rheumatoid arthritis.1,3

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We report a case of BCG associated with seronegative rheumatoid arthritis in which the articular manifestations of the rheumatoid disease worsened with exacerbations of BCG. This and another recent report suggest that BCG is part of a systemic disease process.

CASE REPORT

A 49-year-old woman with a four-year history of seronegative rheumatoid arthritis with vasculitic skin lesions was otherwise well until the development of a six-week history of a nonproductive cough, recurrent fevers, polyarticular arthritis, and the acute onset of shortness of breath. Temperatures rose to 39.4°C accompanied by chills. Physical examination disclosed fever, tachypnea, tachycardia, with clear lung fields and minimal thickening of the metacarpophalangeal joints. A transtracheal aspirate showed a few leukocytes but no organisms; subsequent cultures gave negative findings. The leukocyte count was 10,000/cu mm, with 69 percent polymorphonuclear leukocytes, and 11 percent band forms with toxic granulations, 19 percent lymphocytes and 1 percent monocytes. The hematocrit reading was 38. Westergren method ESR was 70 mm per hour. The chest roentgenogram (Fig 1) demonstrated three rounded densities, 2 to 5.5 cm in diameter, in the right and left lower lobes and lingula. Electrolyte, BUN, and urinalysis values were normal. Hepatocellular enzyme levels were minimally elevated. Skin tests of PPD and for Candida and Trichophyton all were negative; ANA and rheumatoid factor studies also were negative.

Initial therapy for presumed Legionella and subsequently for tularemia (elevated titers with possible exposure) were without clinical response. Fiberoptic bronchoscopic study revealed hemorrhagic bronchitis with a nondiagnostic transbronchial biopsy. Right thoracotomy revealed a mass involving the right lower lobe extending to the hilum; a 50-ml pus pocket was found in the hilum and no adenopathy was apparent. Gram stain, aerobic and anaerobic cul-

FIGURE 1A (left). Posteroanterior chest roentgenogram on admission. 1B (right). Lateral chest roentgenogram on admission. Bilateral lesions can be seen. The clips in the left upper mediastinum are from previous thyroid surgery.
Pathologic examination revealed both acute and organizing bronchopneumonia, abscess formation, fibrosis, lipid pneumonia, and focal granulomatous inflammation. Subsequent review of the pathologic specimen (reviewed by Dr. Carrington at Stanford University and Dr. Cowart at the Armed Forces Institute of Pathology) found no evidence of fungi and suggested that the changes were consistent with BCG. The lesion was a bronchocentric process with destruction and replacement of the bronchial wall by palisaded histiocytes around large collections of neutrophils in the lumen. Surrounding lung tissue was also destroyed, with secondary involvement of the pulmonary arteries. Postoperatively the patient remained febrile despite antibiotic therapy. She was given prednisone, 60 mg/day, and had rapid defervescence and clearing of symptoms. Unfortunately, while receiving high-dose prednisone, she manifested hyperglycemia and glycosuria. The chest roentgenogram showed improvement, but the changes noted were related more to the postoperative healing and resolution of the infectious process. The rounded densities remained unchanged.

During the subsequent 47 months following diagnosis, she has felt generally well but has had persisting exertional dyspnea, nonproductive cough, arthralgias, and vasculitic lesions on her fingers and elbows. Biopsy findings of these lesions were consistent with leukocytoclastic vasculitis. Steroid therapy was tapered to discontinuation on three occasions with exacerbation of her arthritic and vasculitic symptoms (skin lesions), as well as the development of cough and hemoptysis, all of which cleared with reinstitution of steroid therapy. An ill-defined lingular infiltrate, which improved slightly over an eight-month period but never cleared when the prednisone dosage was increased to 60 mg per day, accompanied the episode which was severe enough to require rehospitalization. Chlorambucil was given up to 8 mg/day with some improvement, but had to be discontinued due to pancytopenia. On one occasion, when chlorambucil therapy was stopped and prednisone was being given at 15 mg/day, she complained of congestion in her chest with wheezing. At that time wheezes were heard over the right posterior upper lung field on quiet breathing, but they cleared following a forced expiratory maneuver.

**DISCUSSION**

The disorders that result in pulmonary granulomatosis with no apparent infectious cause have similar clinical, pathologic, and radiologic presentations. The histologic similarity to the hypersensitivity granuloma suggests an autoimmune etiology. However, no antigens have been identified as causal, and immunologic mediators are variably present. BCG is characterized by the involvement of bronchi and bronchioles with an inflammatory and granulomatous reaction that only incidentally involves pulmonary vessels. Katzenstein et al proposed that BCG resulted from an immunologic reaction to endobronchial Aspergillus or other fungi. They were able to identify Aspergillus in bronchial secretions and precipitating antibodies in many of those cases associated with asthma, as have others. However, antigens could be identified in only a minority of patients with coincident asthma and in none of the nonasthmatic patients. Our patient had no histologic or culture evidence of fungus.

The repeated occurrence of arthralgias and vasculitis during exacerbations of BCG noted in our patient has not been previously described in subjects with BCG to our knowledge. The symmetric articular pain and swelling involving her hands, shoulders, and knees is compatible with seronegative rheumatoid arthritis, despite the lack of destructive changes. Rheumatoid factor and ANA were negative in eight of eight and six of six cases, respectively, in the study by Katzenstein et al. Koss et al specifically noted the lack of clinical or laboratory evidence of rheumatologic disease in 15 patients. In his series of 17 patients, Saldana reported that one patient had rheumatoid arthritis. Of interest is the brief mention of the occurrence of "striking" BCG lesions in two patients with rheumatoid arthritis. Recently, a case report of BCG with scleritis was reported, which, to our knowledge, is the first suggestion that BCG may be part of a systemic disease process. Our patient's characteristics also raise the possibility that BCG is not a distinct disease entity, but part of a more generalized disorder.

The etiology of BCG is not known at this time. The occurrence of extrapulmonary symptoms may represent two coincident diseases, or both may have a common immunologic basis. In this patient BCG may be one of the manifestations of the disease called seronegative rheumatoid arthritis. Further understanding of BCG will require clinical, immunologic, and pathologic characterization of all cases.

**REFERENCES**