Bronchiectasis and Homozygous Alpha1-Antitrypsin Deficiency

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A 34-year-old woman with homozygous alpha1-antitrypsin deficiency suffered from progressive, generalized cystic bronchiectasis. Although bronchiectasis was reported in the original monograph on the enzyme inhibitor deficiency, it has received minimal attention since then. Alpha1-antitrypsin levels should be measured in patients with severe bronchiectasis.

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Since the observations of Laurell and Eriksson\(^1\) in the mid 1960's, and subsequently by numerous other groups,\(^3-6\) the association of alpha,-antitrypsin deficiency with pulmonary emphysema has become well known. More recently an association of this deficiency with cirrhosis, both infantile and adult,\(^7-9\) has been established.

We have recently treated a patient with diffuse, severe bronchiectasis associated with homozygous alpha,-antitrypsin deficiency.

**CASE REPORT**

A 34-year-old woman of British descent presented in 1973 complaining of increased sputum production, fever and nausea. She had pertussis at age two but experienced no respiratory symptoms until 1963 when she had the onset of nocturnal pleuritic chest pain and a nonproductive cough. Two months thereafter she developed the first of several episodes of fever associated with productive cough and lower lobe infiltrates. In 1964, bronchography revealed severe cystic bronchiectasis involving the entire bronchial tree bilaterally (Fig 1). Between 1965 and 1973, she suffered numerous episodes of increased bronchial infection, hemoptysis, consolidation of various lobes and purulent sputum production to 400 ml a day. Since 1968, she had experienced a progressive increase in exertional dyspnea.

She smoked less than one-half pack of cigarettes a day intermittently between 1959 and 1970. Family history revealed that one maternal uncle and two maternal aunts, all cigarette smokers, had emphysema or bronchitis. There was no family history of bronchiectasis, cystic fibrosis or liver disease.

Examination revealed her to be febrile and to appear chronically ill, weighing 49 kg. Diffuse bronchial breath sounds and coarse inspiratory rales over the lower half of her chest were heard. Her fingers were clubbed without nail cyanosis. The remainder of the examination was normal.

Chest roentgenogram revealed diffuse pulmonary scarring with numerous cavities, typical of bronchiectasis (Fig 2). Serum electrophoresis revealed decreased alpha\(_1\) globulin (0.1 g per 100 ml). The \(\alpha_1\)-antitrypsin concentration was less than 50 mg per 100 ml (normal 200 mg). Characterization revealed a \(\text{Pi} \, \text{ZZ}\) phenotype and a serum 

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\text{alamin} \quad 0.215 \text{ units (normal >0.85 units).}
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Sweat sodium content was 60 mEq per liter. Aerobic sputum cultures revealed throat flora. Results of immunoglobulin assays, urinalysis, hemoglobin, leukocyte count, blood urea nitrogen, fasting blood sugar, alkaline phosphatase, bilirubin, serum glutamic oxaloacetic transaminase, tuberculin skin test and electrocardiogram were normal.

The patient was subjected to bronchoscopy which revealed numerous pus-filled, cystic cavities; 200 ml of purulent material was aspirated. Treatment with antibiotics, humidification, intermittent positive pressure breathing with bronchodilator and chest physiotherapy resulted in improvement. Pulmonary function tests revealed (predicted values in parentheses): forced vital capacity, 2.04 liters (3.05 liters); one second vital capacity, 1.35 liters (2.44 liters); three second vital capacity, 1.80 liters (2.96 liters); maximum midexpiratory flow rate, 0.79 liters per second (3.15 liters per second); maximum voluntary ventilation, 44 liters per minute (79 liters per minute); inspiratory capacity, 1.30 liters (1.70 liters). A modest response to bronchodilator occurred. Further tests revealed: helium method total lung capacity (TLC), 5.21 liters (3.66 liters); residual volume (RV), 3.25 liters (1.12 liters); RV/TLC, 60.3 percent (30.6 percent); helium equilibration time, 120 seconds (less than 90 seconds); \(P_{\text{O}_2}\), 66 mm Hg; oxygen saturation, 93.2 percent; \(P_{\text{CO}_2}\), 47 mm Hg; pH, 7.41; bicarbonate, 29.9 mEq per liter; base excess, 4.8. The \(P_{\text{O}_2}\) fell to 57 mm Hg with exercise and rose to 405 mm Hg on 100 percent oxygen.
DISCUSSION

Generalized cystic bronchiectasis is an uncommon disease. It is not generally thought to be part of the spectrum of, nor secondary to, chronic obstructive lung disease. The diseases which most commonly lead to secondary, severe bronchiectasis include mucoviscidosis, immunoglobulin deficiencies, pertussis, influenza, measles and other viral pneumonias, aspiration, and recurrent bacterial pneumonias. There is also a well-known association with sinusitis and/or dextrocardia. The occurrence of bronchiectasis in our patient with homozygous α1-antitrypsin deficiency prompted us to review the association between these two entities.

Upon examination it appears that the relationship between α1-antitrypsin deficiency and generalized bronchiectasis is well documented but has received minimal attention. Indeed two of Eriksson’s original 23 patients had clinically severe, diffuse bronchiectasis as a prominent part of their illness. As noted by Falk and Smith, the classic description of a smoker developing severe, “dry,” panacinar emphysema in the third or fourth decade is too restrictive. In a comparison of a large group of patients with severe pulmonary emphysema, Hutchinson and associates found chronic bronchiectasis in 62 percent of those with homozygous deficiency versus 70 percent of those with no deficiency—an insignificant difference. Bronchiectasis, although much less common, appears to represent another portion of the spectrum of pulmonary complications found with this deficiency. We want to emphasize that, in our patient, clinical and roentgenographic manifestations of severe bronchiectasis (copious, purulent sputum production and hemoptysis, recurrent pulmonary infection, and multiple cystic cavities with air-fluid levels) were the dominant features of her illness for several years prior to the onset of dyspnea and still represent the most difficult management problems.

The pathogenesis of bronchiectasis in this setting has not been completely resolved. As summarized by Lieberman, much of the current thinking regarding the development of pulmonary disease in these patients revolves around the knowledge that α1-antitrypsin inhibits a multitude of proteolytic enzymes, such as trypsin, elastase, bacterial and leukocyte proteases, chymotrypsin, and possibly many others. It is postulated that the protease inhibitory capability of human serum protects the lung from injury, especially during periods of inflammation or infection, when there are likely to be high local concentrations of proteases. If this protective capacity is deficient, the pulmonary parenchyma becomes more susceptible to destruction.

In light of this hypothesis, the histopathologic observations of Glasgow et al are very intriguing. They noted, in their one necropsy specimen, diffuse bronchial and bronchiolar dilatation as well as panacinar emphysema. The elastic lamina was not intact in any of the bronchi examined and was totally absent from the walls of many of the specially stained specimens. It is certainly attractive to postulate a similar mechanism operative in our patient, who had pertussis in childhood. That is, in the presence of underlying α1-antitrypsin deficiency, a childhood infection led to destruction of bronchial walls and subsequent bronchiectasis.

We cannot be absolutely sure our patient’s enzyme inhibitor deficiency caused her bronchiectasis. However, the rarity of these two conditions separately and the previously reported occurrence of the two entities together, strongly point to an association between them. Since most patients with bronchiectasis are probably not screened for the enzyme inhibitor deficiency, the frequency of its presence in such patients is unknown. α1-antitrypsin levels should be measured in patients with severe bronchiectasis.

REFERENCES