Bronchiectasis in Patients With α₁-Antitrypsin Deficiency*
A Rare Occurrence?

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The chest radiographs and computed tomographic (CT) scans of seven patients with homozygous proteinase inhibitor phenotype Z (PiZZ) α₁-antitrypsin deficiency were reviewed. All patients except one showed severe emphysema with or without bullous change. Bronchiectasis was detected in three patients by CT but only in two patients by chest radiography. A young patient developed bronchiectasis before symptomatic emphysema. We stress that patients with PiZZ are susceptible to bronchiectasis, and the widespread use of CT should reveal its true incidence which might not be as low as generally believed.

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Pizz = proteinase inhibitor phenotype Z

It is generally believed that patients with α₁-antitrypsin deficiency suffer from pulmonary emphysema but rarely from bronchiectasis. Indeed, most individuals who are homozygous proteinase inhibitor phenotype Z (PiZZ) develop severe panlobular emphysema, predominately at the lung bases, in the third and fourth decades of life. The cardinal clinical symptom is progressive dyspnea with minimal cough. Some individuals, particularly those who smoke, also develop chronic bronchitis. α₁-antitrypsin deficiency, however, is considered to be a rare cause of bronchiectasis. During the past 5 years, we have encountered seven patients with PiZZ phenotype. All of them complained of progressive dyspnea. Four of them also suffered from chronic cough with sputum production. Bronchiectasis was detected in three patients. We would like, therefore, to stress that patients with PiZZ are also subject to development of bronchiectasis. Its incidence is not as low as commonly thought due to the use of improved roentgenographic technology, such as CT, for its detection and better health care for prolongation of life. Since six of the seven patients were on the waiting list for lung transplantation, the detection and localization of bronchiectasis are important for pretransplant evaluation, especially in making the decision as to which lung to replace.

Methods

Patients

The clinical symptoms and chest radiographic findings of seven patients with α₁-antitrypsin deficiency were summarized in Table 1. The patients were examined at the University of Alabama Hospital, Birmingham, during the last 5 years. The patients, four women and three men, were all adults ranging in age from 21 to 56 years. The initial diagnosis of α₁-antitrypsin deficiency was made by measurement of its concentration in serum by either electrophoresis or its activity in serum.

Table 1—Clinical and Chest Radiographic Findings in Seven Patients with α₁-Antitrypsin Deficiency (PiZZ)

<table>
<thead>
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<th>Subject</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Radiographic Findings</th>
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| 1       | 36/M    | Progressive dyspnea since age 28  
Minimal cough | Diffuse emphysema, more severe in lower lobes |
| 2       | 40/F    | Progressive dyspnea since age 20  
Minimal cough | Severe emphysema, particularly in both lower lobes |
| 3       | 47/M    | Onset of dyspnea at age 30  
Improved after quitting smoking  
Recurrence of dyspnea at age 40  
Occasional coughs with white-yellow sputum | Mild emphysema, pleural adhesions, and old rib fracture |
| 4       | 55/M    | Progressive dyspnea for many years  
Repeated bronchitis with yellow sputum | Hyperinflation with bullous changes, area of fibrosis (healed pneumonia) |
| 5       | 52/F    | Progressive dyspnea since young age  
Chronic cough productive of copious purulent sputum | Marked hyperinflation with bullous changes, more in lung base, saucular bronchiectasis, lower lobes |
| 6       | 21/F    | Adenoviral pneumonia at age 1½  
Haemophilus influenzae pneumonia at age 12,  
progressive dyspnea, recent years | Severe emphysema with bullous changes, more marked in the left, bilateral bronchiectasis, right side by CT only |
| 7       | 56/F    | Progressive dyspnea for many years  
Chronic cough with yellow sputum  
Repeated pneumonia | Hyperinflation, more severe in lower lobes, bronchiectasis, lower lobes, by CT only |

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phoresis or nephelometry. The serum α₁-antitrypsin levels of these seven patients were less than 10 to 15 percent of the normal and often near zero. The establishment of diagnosis was followed by phenotyping by isoelectric focusing which indicated PiZZ phenotype in all patients. Progressive dyspnea was the predominant symptom in all patients. Three patients (cases 1, 2, and 6) had minimal cough, while the remaining four patients suffered also from chronic bronchitis as defined by cough with expectoration for at least 3 months of the year for more than two consecutive years. These four patients with chronic bronchitis all had a history of tobacco smoking. Case 6 contracted adenoviral pneumonia at age 1 1/2 years, Haemophilus influenzae pneumonia at age 12, and developed progressive dyspnea only in recent years. Cystic fibrosis was ruled out in this young patient by negative sweat test. None of the seven subjects had evidence of immunoglobulin deficiency.

Each patient had a number of conventional chest radiographic studies. The CT scans were performed with a scanner (GE 9800, Philips TX60, or Picker 1200) at continuous 10-mm thickness with a 5-s scan time. Additional high-resolution scans were obtained with 1.5-mm collimation and high-spatial-frequency reconstruction algorithm at selected levels (aortic arch, carina, and diaphragm) in three patients.

RESULTS

Both conventional radiography and CT showed

Figure 2. Thoracic CT of case 6 at a level below carina showing cystic bronchiectasis in the right lung.

Figure 3. Thoracic CT of case 6 showing mild cylindrical bronchiectasis in the left lower lung which is not detected on chest radiograph.

hyperinflation of the lung in all seven patients. Such emphysematous changes were severe, especially in the lower lobes, in all patients except case 3 who showed only mild emphysema. Bullous change was also noted in cases 5 and 6. In addition, chest radiography in case 5 showed bilateral cystic or saccular bronchiectasis which was confirmed by CT (Fig 1). In case 6, the chest radiograph also showed cystic bronchiectasis in the left lung which was also confirmed by CT (Fig 2). The milder cylindrical bronchiectasis in the right middle and lower lobes was demonstrated on CT (Fig 3) but not on the conventional radiograph. In case 7, bronchiectasis was also demonstrated only on CT but not on chest radiographs.

DISCUSSION

Alpha₁-antitrypsin is a 52-kilodalton glycoprotein with 12 percent carbohydrate, synthesized and secreted by the hepatocytes, has a high plasma concentration, very broad range of antiprotease (or antielastase) activity, and is an acute phase reactant. The α₁-antitrypsin gene has been mapped to the distal portion of the long arm of chromosome 14. The two α₁-antitrypsin genes are codominantly expressed and together define the α₁-antitrypsin level in serum. Most common α₁-antitrypsin alleles are classified as M-type. There are more than 75 known pleomorphic alleles of which at least 20 can cause a clinically relevant deficiency state. The most common and serious "deficiency" mutation is Z as the result of point mutation by replacement of Glu-342 in exon V by Lys. Such substitution of homozygous PiZZ patients leads to aggregation of α₁-antitrypsin in the rough endoplasmic reticulum and impairment of its secretion into the circulation.

Not every person with a homozygous PiZZ state develops symptomatic pulmonary emphysema. A review by Morse indicated that about 70 to 80 percent
of subjects with PiZZ would develop symptomatic emphysema. However, with the wide availability of detection technique, a strong suspicion now exists that the number of patients with asymptomatic α₁-antitrypsin deficiency is greater than those who develop symptomatic emphysema. Neutrophils are the major source of elastase in the lung which damages interstitial elastic fibers leading to emphysematous changes. Any cause such as infection which recruits neutrophils to the lung will upset the elastase-antielastase balance, particularly in patients with α₁-antitrypsin deficiency.10 All our patients were susceptible to the development of emphysema at an early age because of α₁-antitrypsin deficiency. Cigarette smoking is another risk factor since the cigarette smoke is rich in oxidants which can inactivate α₁-antitrypsin.10,11 Four of our seven patients (Nos. 3, 4, 5, and 7) had histories of tobacco smoking.

In addition to symptomatic emphysema, the four patients who smoked also suffered from chronic bronchitis. Typically, they had bouts of cough with copious purulent sputum. Such chronic inflammation (infection) and bronchial obstruction are most frequent conditions associated with bronchiectasis. Chronic inflammation weakens the bronchial wall, and obstruction leads to the bronchial dilation. This is due to the resorption of the entrapped air from the airway distal to the obstruction, resulting in atelectasis. With atelectasis, the elastic forces within the lobe disappear and airways “relax” and dilate. Therefore, subjects with PiZZ may have normal lung, pulmonary emphysema alone (cases 1 and 2), emphysema with chronic bronchitis (cases 3 and 4), and emphysema, chronic bronchitis, and bronchiectasis (cases 5 and 7). It is, therefore, speculated that the severity of lung disease in patients with α₁-antitrypsin deficiency progresses from pulmonary emphysema to chronic bronchitis to bronchiectases. However, this may not always be true. The 21-year-old female patient (case 6) developed cystic and cylindrical bronchiectasis early in her life as the consequence of repeated pulmonary infection which was followed by emphysematous changes. Three similar cases have been previously reported.12 It is conceivable that patients with PiZZ are more susceptible to bronchiectasis especially when exposed to repeated pulmonary infection, even before the development of emphysema. Adenovirus pneumonia at an early age seems to be particularly important since adenovirus has previously been described as a known etiologic agent in severe bronchiectasis.13

Bronchiectasis was not seen on chest radiographs in case 7 nor in the right lung in case 6. Computed tomography is much more sensitive in detection of bronchiectasis, and it also demonstrates the severity and exact location of bronchiectasis. We predict that the wide use of CT should detect more cases of bronchiectasis in patients with PiZZ.

Most of our patients were admitted for evaluation of possible lung transplantation. The detailed examination of pulmonary structure, including the existence, severity, and location of bronchiectasis, is very important. The information can be used for setting criteria for transplantation and also for determining which lung to replace in the case of unilateral lung transplantation.

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