Intermediate Alpha_{1}-Antitrypsin Deficiency with Apical Lung Bullae and Spontaneous Pneumothorax*

Presence of a Z Variant In an American Black

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A 43-year-old black man had an 18-year history of apical lung cystic-bullous disease. Following two episodes of spontaneous pneumothorax and two instances of thoracotomy for bullectomy and pleural abrasion, he was found to have an intermediate AAT deficiency with an MZ phenotype. It is believed that this is the first case of localized bullous lung disease to be reported in association with any degree of AAT deficiency. There is evidence that the cystic lesions progressed to form upper lobe bullae. It is postulated that the AAT deficiency may have played a role in this progression, as did the patient’s cigarette smoking. Following two instances of surgery, CT scans of the lungs, compliance studies and complete pulmonary function tests show no further evidence of bullae or emphysema. The rarity of the Z variant of AAT in blacks is discussed.

(CHEST 1991; 99:1545-46)

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\text{AAT = alpha-antitrypsin; } Dsb = \text{single-breath carbon monoxide diffusing capacity; } TLC = \text{total lung capacity}
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Alpha-antitrypsin deficiency is well recognized as a predisposing factor toward the development of obstructive lung disease, usually panacinar emphysema.1 The Z variant of AAT, which is the most common cause of the deficiency, is quite rare in blacks and has not been reported previously in association with localized bullous lung disease or with spontaneous pneumothorax in any race.

The present report involves a black male patient with an MZ phenotype for AAT associated with localized, bilateral, bullous disease and episodes of spontaneous pneumothorax.

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CASE HISTORY

A 43-year-old black American man was first seen in 1974 with dyspnea on exertion of two years’ duration. He had smoked 1 to ¼ packs of cigarettes per day for ten years. Chest x-ray films in 1974 showed severe bullous emphysema of the right upper lobe and two emphysematous blebs of the left apex. Unfortunately, these x-ray films are not available for reproduction at this time. A perfusion scan showed absence of perfusion of the right upper lobe with decreased perfusion of the apical portion of the left upper lobe. A ventilation scan showed decreased ventilation of both upper lobes, with the right being worse than the left; the washout phase showed retention of tracer in the upper lung fields bilaterally. A Dsb was slightly reduced (65 percent of predicted) but normal when corrected for the diffusion lung volume. Lung spirometry showed only mild restrictive and obstructive changes and normal arterial blood gas levels. The TLC was 5.68 L when measured by plethysmography, but measured 4.88 L by the dilution of helium from the 10-s diffusion capacity measurement; this difference in TLC by the two measurements suggested that the volume of bullae was approximately 0.8 L. A serum protein electrophoresis showed the presence of an alpha-globulin peak measuring 0.1 mg percent which was at the lower limits of normal.

In December of 1974, the patient suffered a spontaneous pneumothorax of the right side of the chest, which responded to therapy with a chest tube. In February of 1975, he was readmitted for elective surgery to include a bullectomy and pleural stripping of the right lung. An angiogram prior to surgery showed normal vasculature to the lower lung fields with absent vasculature in the area of the bullae, and with some compression of the right and left lower lung fields. At surgery, large bullae were found in the right upper lobe along with a few smaller blebs in the right upper lobe as well as in the right middle and lower lobes.

In February of 1989, the patient awoke with pleuritic left chest pain and dyspnea. A chest x-ray film now showed a 70 to 80 percent pneumothorax on the left side. This was treated at another hospital with chest tube reexpansion. After reinfiation, a chest x-ray film then showed a large left apical bulla (Fig 1). At exploratory thoracotomy, multiple blebs and bullae were found in the left upper lobe; these were excised and a pleural abrasion was performed with sterile gauze.

During a follow-up examination in September 1989 at the Sepulveda VA Medical Center Chest Clinic, the patient was tested for his antitrypsin status. He was found to have an intermediate deficiency (AAT concentration, 125 mg percent; severe deficiency, less than 80 mg percent; intermediate deficiency, 80 to 170 mg percent) by radial immunodiffusion (Kallestad Diagnostics; Endo-

![Figure 1. Expiratory chest x-ray showing large left upper lobe bulla with some depression of the left hilar vasculature. Staples from previous right-sided bullectomy are visible.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21629/ on 04/19/2017)
plate. Alpha-1-Antitrypsin Test Kit) and a heterozygous MZ phenotype (Pharmacia/LKB; Ampholine PAG plate; pH, 4.0 to 5.0).

Additional studies were performed to evaluate the patient's pulmonary status following the excision of his lung bullae from both lungs. The pulmonary function test results were as follows: VC, 3.21 L (73 percent); RV, 1.67 L (78 percent); TLC, 4.87 L (78 percent); and FEV1, 2.73 L (77 percent).

Arterial blood gas levels were: pH, 7.42; PaO2, 41.0; and PaCO2, 81.1. The Dsb was 74 percent of predicted. A compliance study showed normal static lung compliance (0.20 L/cm H2O). The CT of the lungs evidenced no pathologic abnormalities. No bullae or signs of emphysema were present. Serum angiotensin-converting enzyme level for sarcoidosis was 32.9 units/ml (normal, less than 35.0 units/ml).

**DISCUSSION**

This case presentation is that of a black man with surgically proven localized upper lobe bullous lung disease resulting in two episodes of spontaneous pneumothorax and associated with an intermediate, heterozygous (MZ) AAT deficiency. The association of this type of lung disease and the MZ phenotype does not prove a relationship between the two, but it is known that antitrypsin deficiency may predispose to pulmonary emphysema.2,3 An association of AAT deficiency with localized bullous lung disease, however, is not established.

A number of studies of AAT in patients with simple spontaneous pneumothorax have been reported.4-7 In none of these was AAT deficiency detected. These cases differ from the current patient being reported in that they involved patients with pneumothorax resulting from small lung cysts, and not from large localized bullous disease. To our knowledge, this is the first case of localized bullous lung disease reported in which either severe or intermediate AAT deficiency has been found. It is of interest, however, that our patient also had cystic disease of the lung which may have progressed to bullous disease. Especially in our patient's left lung, a few small cysts were detected early in the course of the disease, but at the time of the pneumothorax and surgery 15 years later, large bullae were found. In the right lung, both small cysts and large bullae were found at the time of surgery.

The question may be raised as to whether the deficiency of AAT allowed the cysts to progress to bullous disease, since the cystic disease in most cases of spontaneous pneumothorax with a normal AAT do not progress. The damaged, cystic, lung may be more subject to further damage by proteolysis in the presence of AAT deficiency and cigarette smoking.

The presence of the Z variant in an American black subject is also unusual. In a previous study of 186 American blacks, we found none with the Z variant, and Pierce et al8 found a gene frequency of 0.005 (ie, two subjects with the Z variant) among 204 black subjects. Hug et al9 discovered a black family with an AAT variant that moved cathodal to the Z type, but which had normal AAT concentration and activity, unlike the Z variant. They named this allele PiZW. The same investigators also detected other variants with normal levels of AAT activity among American black families which were named PiWalter, PiSlemmer, and PiKeller. They are presented in Table 1. Among blacks from Mozambique and Bantu subject with a Z variant was observed. It should be expected that intermarriage between blacks and whites will eventually increase the prevalence of the Z variant among offspring with dark skin.

Controversy still exists regarding the role of the intermediate AAT deficiency state as a predisposing factor to the development of lung disease.8,10,11 It is now generally agreed, however, that cigarette smoking can cause a relative imbalance between inflammatory proteases and antiprotease activities and that a reduced baseline of AAT activity as is present in those with the intermediate (heterozygous) AAT deficiency state may further jeopardize the balanced state. In our patient, following surgical excision of the apical bullae, the remaining lung function appears to be entirely normal except for some restrictive changes probably related to surgery. No evidence of generalized emphysema is observed by CT scan, compliance studies, pulmonary function or Dsb. Thus, a protective effect by the intermediate level of AAT is apparent in this patient. Long-term follow-up studies of this patient will be of great interest.

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