Lung Volume Reduction Surgery for Patients with Alpha-1 Antitrypsin Deficiency Emphysema

James M. Donahue, MD[a], Stephen D. Cassivi, MD, MSc, FRCSC[b,c,*]

KEYWORDS

• Emphysema • Surgery • Alpha-1 antitrypsin deficiency
• Lung volume reduction surgery

Alpha-1 antitrypsin deficiency (A1AD) is a rare genetic disorder characterized clinically by early-onset emphysema and, more rarely, liver disease and vasculitis. Recent advances in understanding the genetic basis of this disorder have enabled a more detailed understanding of its epidemiology. Alpha-1 antitrypsin is a serine protease inhibitor whose major function is to counteract the proteolytic activity of neutrophil elastase and trypsin. In the lungs, enhanced elastase activity results in accelerated parenchymal destruction leading to emphysematous changes predominantly in the lung bases. Medical treatment for this disorder includes standard therapies for emphysema and so-called augmentation therapy, consisting of the infusion of purified pooled plasma alpha-1 antitrypsin. Surgical options include lung transplantation and lung volume reduction surgery (LVRS). Although survival rates for patients who have A1AD after transplantation may approximate those of patients who have chronic obstructive pulmonary disease (COPD), donor availability limits its applicability. As with patients who have severe COPD, LVRS has been attempted in patients who have A1AD. The results of these studies form the basis for this review.

INCIDENCE AND PATHOPHYSIOLOGY

A1AD was first described in 1963 by Laurell and Eriksson at Lund University, Sweden.[1] Since that time, extensive population-based and molecular genetic research has enhanced the understanding of the epidemiology of A1AD. The estimated prevalence of A1AD is approximately 1.9% among patients who have emphysema. Accordingly, in the United States, the number of people who have symptomatic emphysema resulting from A1AD is believed approximately 60,000.[2–4]

A1AD is inherited in an autosomal codominant fashion. Approximately 100 separate alleles have been identified in the serine protease inhibitor gene, SERPINA1 (formerly called P_1) on the long arm of chromosome 14 (14q32.1).[5] The most common mutation gives rise to the Z allele and is caused by a glutamate to lysine mutation at position 342. This results in quantitative and functional deficiencies in alpha-1 antitrypsin such that patients who are homozygous ZZ typically produce only 10% to 15% of normal amounts of the protease inhibitor. People of northern European or Saudi Arabian ancestry have the highest rate of this genetic variant. Studies directly measuring the frequency of the ZZ genotype estimate its prevalence in the United States to be 1 in 4455, or approximately 66,000 individuals.[6–8]

Alpha-1 antitrypsin, a serine protease inhibitor, inactivates proteolytic enzymes, primarily neutrophil elastase and trypsin. In addition, alpha-1 antitrypsin has been shown to have anti-inflammatory properties, such as regulating the expression of

[a] Division of General Thoracic Surgery, University of Maryland, 22 South Greene Street, N4E35, Baltimore, MD 21201, USA
[b] Division of General Thoracic Surgery, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905, USA
[c] William J. von Liebig Transplant Center, Mayo Clinic, Rochester, MN 55905, USA
* Corresponding author. Division of General Thoracic Surgery, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905.
E-mail address: cassivi.stephen@mayo.edu (S.D. Cassivi).

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pro-inflammatory cytokines.[9–11] It is produced primarily in the liver and reaches the lungs by diffusion from the circulation, although there is some local production of alpha-1 antitrypsin by macrophages and bronchial epithelial cells in the lungs.[12,13] Deficiencies in alpha-1 antitrypsin lead to accelerated pulmonary parenchymal destruction mediated by unopposed proteolytic action of neutrophil elastase and trypsin.

PRESENTATION AND MEDICAL THERAPY

Patients who have emphysema caused by A1AD generally develop onset of symptoms in the fourth or fifth decade. Despite this relatively early age of presentation, distinguishing patients who have A1AD from those who have COPD can be challenging. Distribution of the emphysematous changes in patients who have A1AD is panacinar and typically disproportionately affects the lung bases (**Figs. 1** and **2**).[14] Patients who have A1AD may, however, also develop emphysematous changes in an apical distribution. A recent study by Parr and colleagues[15] reported that more than one third of patients who had A1AD had an apical predominance of disease. Furthermore, as detailed in the National Heart, Lung, and Blood Institute (NHLBI) registry of patients who have A1AD, symptoms and presentation are similar to those experienced by most patients who have COPD.[16] These areas of overlap with COPD may explain why patients who have A1AD can experience a delay in diagnosis of up to 7 years from the onset of symptoms and why only 1% to 5% of patients who have severe A1AD are believed to be diagnosed accurately.[8,17–19] Although most patients who have A1AD develop emphysema, up to 20% do not.[6,15]

Cigarette smoking is particularly hazardous for patients who have A1AD. Beyond the nonspecific inflammatory reaction that it causes in the airway and lung parenchyma, cigarette smoke also is known to directly inactivate alpha-1 antitrypsin by oxidizing methionine residues to sulfoxyl groups. Avoidance of cigarette smoking, therefore, is critical to averting accelerated disease progression. Data from the NHLBI registry show that the annual rate of decline in the forced expiratory volume in 1 second (FEV_1) in patients who have A1AD was 109 mL/year for smokers whereas it was 67 mL/year for never smokers and 54 mL/year for exsmokers.[16]

Perhaps the most important reason for accurately diagnosing patients who have A1AD is the potential improvement derived from infusion of purified plasma alpha-1 antitrypsin. The goal of augmentation therapy is to maintain serum alpha-1 antitrypsin levels above 11 μmol/L. Levels below this value have been shown to be associated with the development of symptomatic emphysema.[20] Generally, infusions must be administered on a weekly basis to maximize effectiveness. Although proved safe, augmentation therapy is expensive, with costs approximating $50,000 per year.[21] In terms of efficacy, observational data from the NHLBI registry suggest an improvement in survival rates and decrease in the decrement in FEV_1, most notably for patients who have moderate airflow obstruction.[22] Benefits for patients who have severe or mild airflow

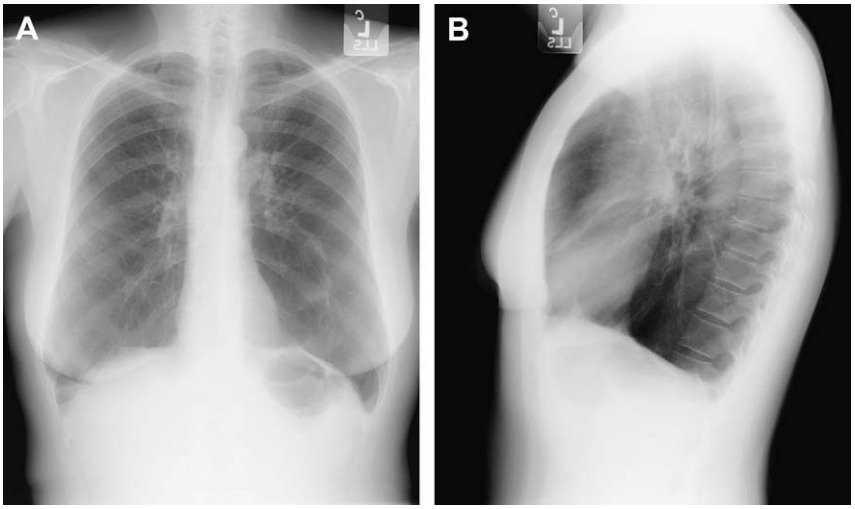

Fig. 1. Typical chest radiograph of a patient who had A1AD emphysema, demonstrating the hyperexpansion of the lungs, flattening of the domes of the diaphragm, and lower lung field predominance of the disease. (*A*) Posterior-anterior view; (*B*) lateral view.