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Case Report

Alpha-1 antitrypsin deficiency associated with rare *SERPINA1* alleles p.(Phe76del) and p.(Asp280Val): A family study

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ABSTRACT

This report describes family members with alpha-1 antitrypsin (AAT) deficiency arising from two rare alleles of *SERPINA1* – p.(Phe76del) and p.(Asp280Val) along with the more common deficiency allele, Pi*Z. The index case, a 51-year-old female presented with cough, bloody sputum, fever, weight loss and night sweats. In addition to a respiratory infection, scans revealed bronchiectasis and bronchiolitis without emphysema. Her AAT level was 30 mg/dL and genetic testing revealed a Pi*Z/p.(Phe76del) genotype. Follow up testing of her relatives revealed the rare p.(Asp280Val) variant as well. AAT deficiency remains underdiagnosed. Early detection and intervention could improve quality of life and outcomes.

1. Introduction/background

Alpha-1 antitrypsin (AAT) is a glycoprotein (52 KDa) that is primarily synthesized in the liver and is transported to the lungs via the cardiovascular system. In lung tissue, AAT serves as a modulator of elastase activity and, in particular, neutrophil elastase (NE). When the homeostasis between AAT and NE is disrupted, as in AAT deficiency (AATD), elastase activity predominates resulting in lung tissue damage and dysfunction.

AAT is coded for by the *SERPINA1* gene. The most common allele of *SERPINA1* is the M-allele which is associated with normal serum levels of AAT. The most common alleles associated with decreased AAT levels are the S- and Z-alleles which are associated with 40 % and 90 % reductions in serum AAT, respectively [1]. In addition to these two common pathogenic alleles, over 500 additional genetic variants of *SERPINA1* have been identified [2].

Depending on the genetic background, the mutation p.(Phe76del) leads to one of the following rare variants: Pi*MMalton (M2), Pi*MPalermo (M1Val), Pi*MNichinan (V) or Pi*Q0LaPalma (S) [1] Clinical reports on patients with a p.(Phe76del) variant in combination with the Pi*Z generally showed serious lung dysfunction while reports on patients that showed this mutation in combination with Pi*M showed mixed lung and liver dysfunction [3,4].

The p.(Asp280Val) mutation, which is associated with Pi*PLowell (M1Val); Pi*PDuarte (M4), Pi*YBarcelona (p.Pro39His) [1], has not been associated with significantly reduced AAT levels except when heterozygous with a severe deficiency allele. The p.(Asp280Val) variant when expressed with another deficiency variant, was associated with increased risk of pulmonary disease [5]. Interestingly, although p.(Asp280Val) was linked to lower levels of serum AAT, the enzyme present was functioning normally [6].

Bronchiectasis has been reported to be a frequent manifestation of AATD especially in individuals with Pi*ZZ genotype [7]. However, the nature and prevalence of bronchiectasis in AATD has not been extensively studied [8]. A recent study of 505 patients with

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the Pi*ZZ genotype found that 9.1 % of these patients had bronchiectasis alone and that bronchiectasis was present in 27 % of the emphysema patients [8].

In this article, we describe the clinical characteristics of a family in which three AAT variants were identified: the more common Pi*Z-variant, and the rare variants p.(Phe76del) - and p.(Asp280Val). The index case has the genotype Pi*Z/p.(Phe76del) and was found to have bronchiectasis without emphysema.

2. Clinical case presentation

Written informed consent was obtained from all participants in this study to allow their de-identified information to be used in this article. Approval from the University of Regensburg Ethics Committee was not requested since the university does not require ethics committee approval for the reporting of individual patient cases. This study was completed in compliance with the Helsinki Declaration (2013 Revision) and all applicable local and national regulations.

The initial patient (index case) was a 51-year-old, Caucasian female of Turkish descent that was initially seen at Krankenhaus Barmherzige Brüder in Regensburg, Germany in August 2022 with the following symptoms: cough, bloody sputum, fever, weight loss and night sweats. The patient has never been a smoker. Initial lung function tests and arterial blood gases were within normal limits: forced expiratory volume in 1 s (FEV1) 78 %, FEV1/forced vital capacity (FVC) 77 %, total lung capacity (TLC) 114 % and diffusing capacity of the lungs for carbon monoxide (DLCO) 104 % (Table 1).

After the patient had a bronchopulmonary infection that was resistant to a macrolide antibiotic, further tests (including computed tomography) revealed that the patient had bronchiectasis and bronchiolitis especially in the lower right lobe without emphysema (Fig. 1). The patient was negative for eosinophils, exhaled nitric oxide, anti-neutrophil cytoplasmic antibodies (ANCA) and tuberculosis. Levels of immunoglobulin subclasses (A, E, M and G) were within normal limits.

Bronchoalveolar lavage revealed granulocytosis and evidence of a *Haemophilus influenzae* infection which was treated with amoxicillin/sulbactam. Eight months later there were further exacerbations of the patient's pulmonary symptoms with evidence of a *Pseudomonas aeruginosa* infection. This infection was successfully treated with 14 days of piperacillin/tazobactam and ciprofloxacin.

The AAT level in this patient was 30 mg/dL, well below the protective threshold of 50 mg/dL [9]. Genetic testing (Alpha ID, Grifols, Barcelona, Spain) of the index patient revealed that the patient was compound heterozygous for the *SERPINA1* gene: Pi* Z/p.(Phe76del). Genotyping was performed at the German AAT Laboratory at the University of Marburg using the Progenika AAT Genotyping Kit (Progenika Biopharma, SA, Derio, Spain) which can simultaneously identify 14 deficiency variants of the *SERPINA1* gene based on Luminex xMAP technology (Luminex Corporation, Austin, TX, USA). The laboratory methods are described in detail elsewhere [10].

As a follow-up to the patient's AATD diagnosis, several family members were screened for *SERPINA1* mutations (Fig. 2). In addition to the Pi*Z variant, the two rare variants p.(Phe76del), and p.(Asp280Val) were also found. The patient's mother (84 years old) was found to have the Pi*MZ genotype and has had a persistent cough for years and suffers from dyspnea on exertion. Both of the

Table 1
Spirometry results for the index patient at diagnosis.

	Target	Result	% Target
Body Plethysmography			
TLC (L)	4.97	5.67	114
VC In (L)	3.12	1.77	57
TGV (L)	2.70	4.00	148
RV (L)	1.75	2.92	167
RV/TLC (%)	35.96	51.44	143
Raw eff (kPa*s/L)	0.30	0.21	70
sRaw eff (kPa*s)	0.96	0.84	87
FVC (L)	3.47	2.75	79
FEV1 (L)	2.78	2.16	78
FEV1/FVC (%)	80.52	78.45	97
PEF (L/s)	6.35	4.87	77
MEF 75 (L/s)	5.60	4.63	83
MEF 50 (L/s)	3.90	2.68	69
MEF 25 (L/s)	0.92	0.71	78
FIV 1 (L)	–	1.51	–
Helium/Carbon monoxide (Single Breath)			
DLCO (mmol/min/kPa)	7.09	7.35	104
KCO (mmol/min/kPa/L))	1.46	1.60	110
VI (L)	3.12	2.03	65
TLC (L)	4.97	4.78	96
FRC (L)	2.70	3.47	128
RV (L)	1.78	2.26	129

TLC = total lung capacity; VC = vital capacity; TGV = thoracic gas volume; RV = residual volume; Raw = airway resistance; sRaw = specific airway resistance; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; PEF = peak expiratory flow; MEF 75 = maximal expiratory flow at 75 % of FVC; FIV = forced inspiratory volume; DLCO = diffusing capacity of the lungs for carbon monoxide; KCO = transfer factor for carbon monoxide; VI = volume of inhaled gas; FRC = functional residual capacity.

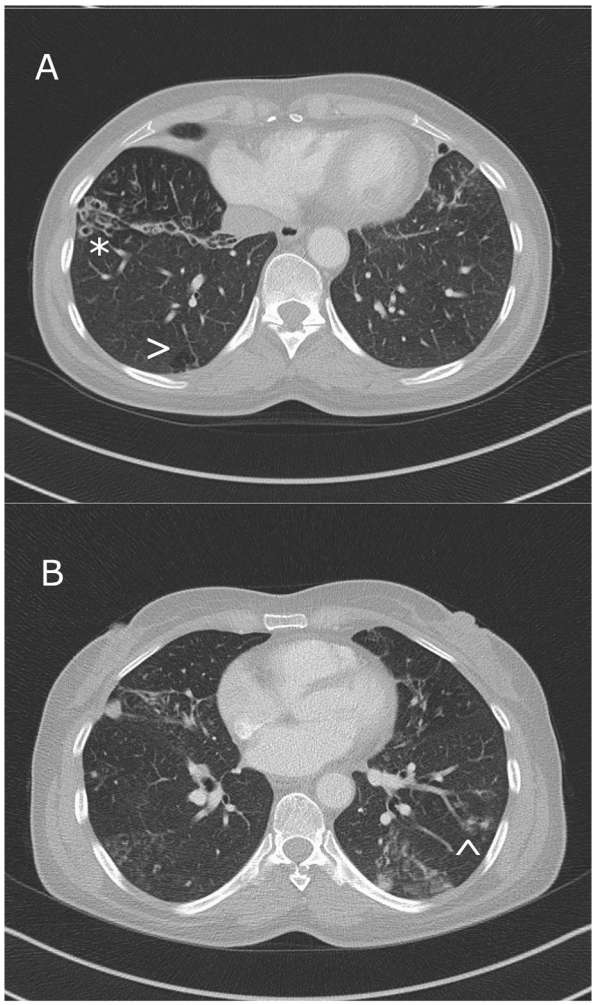

Fig. 1. Transverse CT-scans of the index patient. Scans showing areas of bronchiectasis (*), emphysema (>) in image A and bronchiolitis with tree and bud opacity (^) in image B.

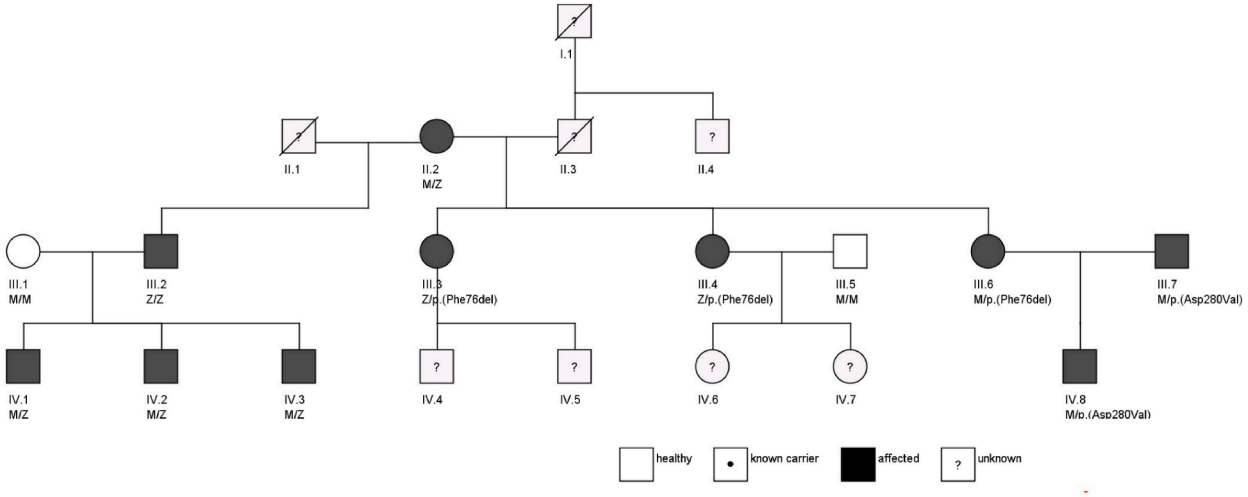

Fig. 2. Genetic screening of family members of the index case (III.3) for *SERPINA1* variants. Circles indicate female family members and squares indicate males.

mother's husbands are deceased and one died at the age of 30 years. Based on available information, the other husband did not have any pulmonary symptoms.

A half-brother (designated III.2 in Fig. 2) is an ex-smoker with a history of a severe, persistent cough, elevated liver enzymes and pancreatitis. One sister (III.4) has the same genotype as the patient (Pi*Z/p.(Phe76del)) and has been diagnosed with ANCA-positive vasculitis. A younger sister (III.6) has the genotype (Pi*M/p.(Phe76del)) has occasional respiratory distress and is extremely sensitive to cigarette smoke. The younger sister's husband (III.7), who is from the same village, has the genotype Pi*M/p.(Asp280Val) and was diagnosed two years ago with chronic obstructive pulmonary disease (COPD). His father has COPD as well.

The patient's children and nieces (IV.4-IV.7) are currently living in Germany and have not been tested for insurance reasons. They are aware of the hereditable nature of AATD and all are non-smokers.

3. Discussion

AATD is an underdiagnosed, and, consequently, an undertreated disease. Screening of patient populations that are potentially AAT deficient is important so that patients with AATD could reap the potential benefits of early therapeutic intervention (e.g., smoking cessation and AAT augmentation therapy). These benefits could include slowing of disease progression. A recent longitudinal study demonstrated that AAT replacement therapy decreased the deterioration of lung function in patients with less severe disease (GOLD Stage 2) and decreased overall mortality in the AATD population studied [11].

The case reported here is remarkable for its phenotypic presentation. This patient had pulmonary infectious symptomology with bronchiectasis but without significant emphysema. Greulich et al. reported that the presence of bronchiectasis was a strong predictor of the Pi*ZZ genotype and advocated AATD testing in patients with bronchiectasis in the absence of emphysema or COPD, i.e., in patients with a similar phenotype to the patient in this case [12].

A recent analysis of the European Bronchiectasis registry (EMBARC) found that AATD was uncommon in the patients included in this network [13]. However, other studies have found a much higher incidence of AATD variants in patients with bronchiectasis not due to cystic fibrosis [14,15]. Conversely, as previously noted, when patients with known AATD in the European Alpha1 Research Collaboration (EARCO) registry were surveyed for bronchiectasis, 9.1 % were found to have bronchiectasis alone and 27 % were found to have bronchiectasis in the presence of emphysema [8]. Based on these studies, current European Respiratory Society guidelines recommend AATD testing in patients that have bronchiectasis without evident etiology [16].

Buck et al. reported beneficial effects of AAT augmentation therapy (decreased exacerbations) in a patient with bronchiectasis and frequent exacerbations [17]. However, at present, there are no prospective, controlled studies supporting this possible method of treatment.

In addition to this case report, only a few other studies report patients with bronchiectasis who were tested and found to have rare AAT variants [18–21]. Clearly additional research on the clinical characterization of rare AAT variants is needed. Based on currently available data it is advisable to test patients with COPD for AATD and to consider testing patients with bronchiectasis of unknown etiology. Patients with rare *SERPINA1* variants should be evaluated and treated individually based on their serum AAT levels and clinical symptoms. Patient education on AATD and possibly referral to a center with AATD expertise may help in making treatment decisions. Genetic testing of family members could help identify relatives with early stage disease who might benefit from therapeutic intervention and young individuals who have not developed symptoms and who could benefit from lifestyle interventions (e.g., smoking prevention or cessation).

4. Conclusion

- The patient identified in this case was compound heterozygous for a rare *SERPINA1* variant p.(Phe76del)and the common deficiency variant Pi*Z and presented with bronchiectasis in the absence of COPD.
- Genetic analysis of her family members revealed several other affected individuals including some with a different rare variant, p.(Asp280Val).
- More widespread testing of selected pulmonary patients could lead to earlier diagnosis of AATD and earlier intervention potentially improving quality of life and outcomes.

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CRediT authorship contribution statement

Marc Lepiorz: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Julius Baier:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. **Martina Veith:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Timm Greulich:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. **Michael Pfeifer:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing.

Declaration of competing interest

ML has received grants from CSL, Grifols and Boehringer Ingelheim. JB reports no competing interests. MV has received grants from Grifols. TG has received grants from Grifols and fees from CSL-Behring, Grifols and Kamada. MP has received grants from Boehringer Ingelheim, Sanofi, Astra Zeneca, and GSK.

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