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Case Report

Pi*M Palermo Mutation in Bronchiectasis due to Alpha-1 Antitrypsin Deficiency: A Rare Genetic Cause

*Alfa-1 Antitripsin Eksikliğine Bağlı Bronşektazide Pi*M Palermo Mutasyonu: Nadir Bir Genetik Sebep*

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ABSTRACT

Bronchiectasis, defined as the permanent dilation of the bronchial wall, is a chronic inflammatory disease with nearly thirty known causes. The most common cause is recurrent and inadequately treated lower respiratory tract infections. Among the rarer causes is alpha-1 antitrypsin (AAT) deficiency, an anti-protease and anti-inflammatory protein deficiency. To date, approximately 500 variants of AAT deficiency have been identified, with the PI*S and PI*Z mutations being the most commonly associated with bronchiectasis. Here, we present a case diagnosed with bronchiectasis secondary to AAT deficiency during an advanced clinical workup, in which the rare Pi*M Palermo mutation was identified. This case is discussed in the context of the existing literature.

Keywords: Alpha-1 antitrypsin, bronchiectasis, M Palermo mutation

ÖZ

Bronş duvarının kalıcı dilatasyonu olarak tanımlanan ve yaklaşık otuza yakın sebebi tanımlanmış kronik enflamatuvar bir hastalık olan bronşektazinin en sık nedeni tekrarlayan, iyi tedavi edilemeyen alt solunum yolu enfeksiyonlarıdır. Bunun dışında görülen nadir sebeplerinden birisi de bir anti-proteaz ve anti-enflamatuvar protein olan alfa-1 antitripsin (AAT) eksikliğidir. AAT eksikliğinin bugün için tanımlanmış yaklaşık 500 varyantı vardır. Bunlar içerisinde PI*S mutasyonu ve PI*Z mutasyonları en sık bronşektazi ile ilişkilendirilmiş varyantlardır. Kliniğimizde bronşektazi ileri tetkiki sırasında bronşektazinin nadir bir nedeni olan AAT eksikliği tanısı alan yine nadir bir mutasyonun (Pi*M Palermo mutasyonu) tespit edilen olgumuz literatür eşliğinde sunulmuştur.

Anahtar kelimeler: Alfa-1 antitripsin, bronşektazi, M Palermo mutasyonu

INTRODUCTION

Alpha-1 antitrypsin (AAT) deficiency is a genetic disorder characterized by low serum levels of AAT due to mutations in the *SERPINA1* gene, which result in impaired production of AAT. AAT is a crucial anti-protease and anti-inflammatory protein known to inhibit the destructive effects of major proteases such as neutrophil elastase. It is a potent serine protease inhibitor (PI) and acts as an acute-phase reactant that protects the lungs from serine proteases, particularly neutrophil elastase. Under normal conditions, PIs neutralize the effects of proteases and help preserve the alveolar architecture. A disruption in the protease/anti-protease balance in the lungs may lead to damaging effects on lung parenchyma. AAT deficiency has been associated with diseases such as bronchiectasis, panacinar emphysema, chronic hepatitis, cirrhosis, and panniculitis[1,2].

The clinical presentation of AAT deficiency most commonly includes emphysema. It remains a subject of debate whether bronchiectasis in these patients is directly associated with AAT deficiency or is secondary to emphysematous changes. Some studies support the theory that bronchiectasis develops secondary to emphysema[3]. It has also been suggested that in AAT deficiency, impaired immune function in the damaged lung through both direct and complex indirect mechanisms may be a critical component in the development of bronchiectasis. Another hypothesis proposes that AAT deficiency may be considered a subcategory of non-cystic fibrosis bronchiectasis, as

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bronchiectasis is observed only in certain subgroups of AAT deficiency[4].

When analyzing the etiology of bronchiectasis, approximately 29 distinct causes can be classified under six major categories (Table 1). Among these, AAT deficiency is considered one of the rarest causes. We present the case of a patient diagnosed with AAT deficiency during the evaluation of widespread bronchiectasis at an advanced age. Genetic analysis revealed the Pi*M Palermo mutation, a rare genetic variant associated with bronchiectasis, which further contributes to the uniqueness of this case.

Table 1. Causes associated with bronchiectasis.

Category	Subgroups
Infections	• **Bacterial:** *B. pertussis, P. aeruginosa, H. influenzae, Mycoplasma, Mycobacterium avium* complex • **Viral:** Measles, HIV, EBV, Influenza, HTLV-1, Herpes simplex virus, Adenovirus types 7 and 21 • **Fungal:** Aspergillosis
Immunodeficiencies	• Primary and secondary immunodeficiency • Complement deficiency • Waldenström macroglobulinemia • Hypogammaglobulinemia • Chronic granulomatous disease
Genetic disorders	• Cystic fibrosis • Alpha-1 antitrypsin deficiency • Williams-Campbell syndrome • Swyer-James syndrome • Mounier-Kuhn syndrome
Clearance defects	• Primary ciliary dyskinesia • Kartagener syndrome • Young syndrome
Systemic diseases	• Rheumatoid arthritis • Sjögren's syndrome • Ulcerative colitis • Crohn's disease • Yellow nail syndrome • Celiac disease
Other causes	• Toxic chemical exposure • Aspiration of gastric contents • Heroin use • Foreign body aspiration • Pulmonary fibrosis • Bronchial tree malformations • Tumor compression

HIV: Human immunodeficiency virus, EBV: Epstein-Barr virus, HTLV-1: Human T-cell lymphotropic virus

CASE REPORT

A 78-year-old female patient presented to the emergency department with complaints of fever, cough, and green-colored sputum. Her medical history included diagnoses of bronchiectasis and hypertension (HT). She had no history of smoking or tuberculosis exposure. The patient was diagnosed with bronchiectasis approximately ten years ago during the evaluation for recurrent lower respiratory tract infections at a healthcare facility. It was also noted that two of the patient's sisters had localized bronchiectasis, suggesting a familial predisposition. On physical examination, early inspiratory crackles were noted in the bilateral mid to lower lung fields. Vital signs were as follows: temperature 39 °C, heart rate 85 bpm, blood pressure 130/70 mmHg, and oxygen saturation 91% on room air, as measured by pulse oximetry. Other systemic examinations revealed no significant findings. Laboratory tests showed elevated acute-phase reactants, with no other remarkable pathological abnormalities (Table 2).

Table 2. Laboratory values of the case.

Parameter	Result	Reference range
WBC (10^3 uL)	**18.2**	4.00-10.00
Neutrophil count (10^3 uL)	**14.55**	2.00-7.00
Neutrophil (%)	**80.2**	40.00-80.00
Lymphocyte count (10^3 uL)	**2.5**	0.80-4.00
Lymphocyte (%)	**13.5**	10.00-50.00
Hemoglobin (g/dL)	10.6	12-16
Hematocrit (%)	33	36.00-47.00
Urea (mg/dL)	37	16.6-48.5
Creatinine (mg/dL)	0.72	0.5-0.9
ALT (U/L)	8	0-33
AST (U/L)	17	0-32
LDH (U/L)	**165**	135-214
CRP (mg/L)	**98.49**	0-5
Procalcitonin (µg/L)	**0.348**	<0.5
Sedimentation (mm/hour)	**47**	0-20
Glucose (mg/dL)	97	74-106
Total bilirubin (mg/dL)	0.4	0-1.2
Uric acid (mg/dL)	6	2.4-5.7
Sodium (mmol/L)	133	135-145
Potassium (mmol/L)	4.8	3.1-5.1
Alkaline phosphatase (U/L)	141	35-104

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, LDH: Lactate dehydrogenase, WBC: White blood cell (Count)

A posteroanterior chest radiograph revealed bilateral diffuse density increases, with cystic lucencies scattered throughout both lungs (Figure 1). Thoracic computed tomography (CT) showed "bilateral tubular cystic bronchiectasis and sequelae of emphysematous changes" (Figure 2).

Further history revealed that two of the patient's sisters had also been diagnosed with bronchiectasis. The AAT levels of both sisters were at the lower limit of the normal range. There was no known diagnosis of cystic fibrosis in the family that could account for the etiology of bronchiectasis, and our patient had no history of infertility. The patient did not recall any severe pulmonary infections during childhood, and no other identifiable causes of bronchiectasis were found. Therefore, serum AAT levels were measured, and the result was 0.29 g/L (reference range: 0.9-2.0 g/L). A medical genetics consultation was requested. Next-generation sequencing of the *SERPINA1* gene revealed a pathogenic variant as shown in Figure 3.

Sputum culture grew *Pseudomonas aeruginosa*, and treatment with piperacillin-tazobactam 4×4.5 g/day was initiated. Acid-fast bacilli testing of the sputum was negative. After clinical improvement, pulmonary function tests were performed; forced vital capacity (FVC) was 1.33 L (92% predicted), forced expiratory volume in 1 second (FEV1) was 2.35 L (68% predicted), and FEV1/FVC ratio was 57%. Diffusing capacity for carbon monoxide could not be measured due to poor patient cooperation.

The patient's overall condition improved, and her symptoms regressed. She was discharged with a diagnosis of AAT deficiency and was referred to the outpatient pulmonology clinic for follow-up. Written informed consent was obtained from the patient.

DISCUSSION

In this report, we present a case of AAT deficiency, which is a rare cause of bronchiectasis that was diagnosed at an advanced age, and which may be overlooked in routine pulmonary clinical practice if not specifically considered.

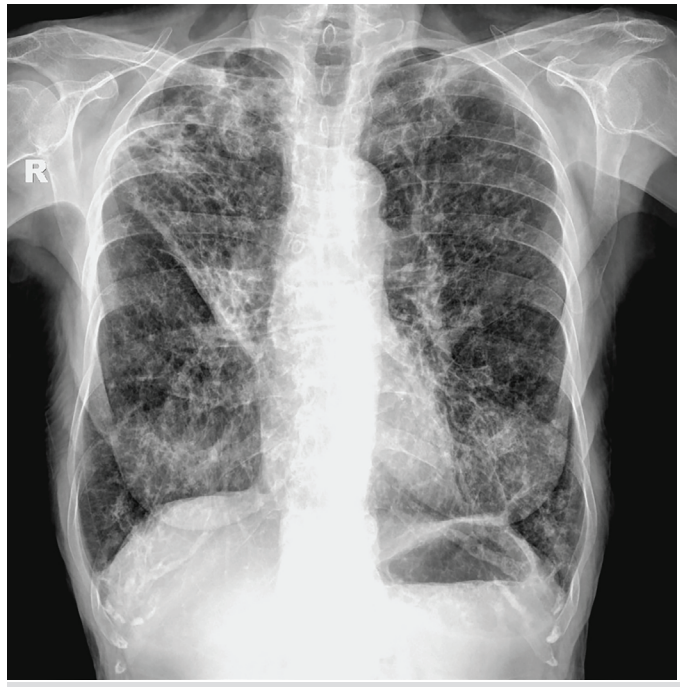

Figure 1. Chest X-ray taken at the time of admission showing increased densities with scattered cystic lucencies throughout all zones of both lungs.

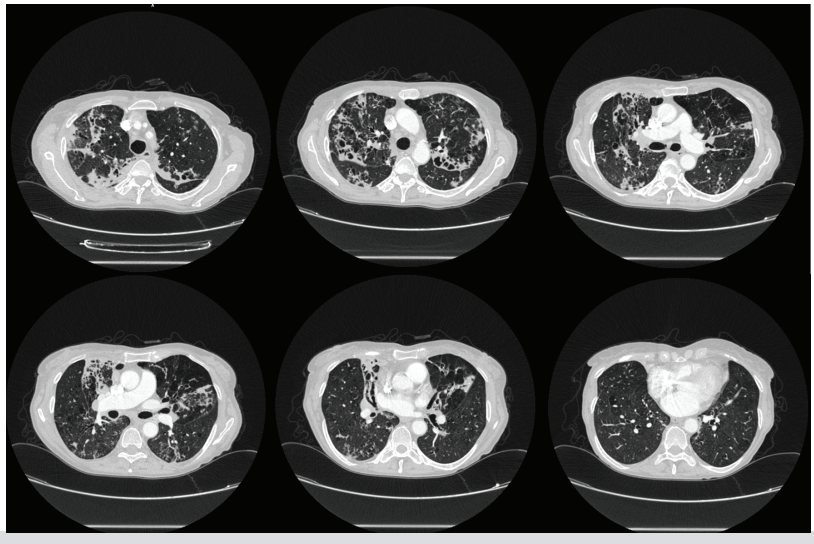

Figure 2. Thoracic computed tomography of the patient revealing bilateral tubular cystic bronchiectasis

Genomic Position	Gene Name / Ref Seq	Effet	Zygosity (Ref/Alt)	Classification
chr14:94849345 GAGA>G rs775982338	SERPINA1 NM_001127701.2 c.227_229del Exon 4/7	inframe_deletion NP_001121173.1 p.Phe76del	HOM 268/1524 VF %85	**Muhtemel Patojenik** PS3,PM4,PP5
Genomic Position	**Gene Name / Ref Seq**	**Effet**	**Zygosity (Ref/Alt)**	**Classification**
chr14:94849348 A>G rs1555369172	SERPINA1 NM_001127701.2 c.227T>C Exon 4/7	missense_variant NP_001121173.1 p.Phe76Ser	HET 159/68 VF %30	VUS PM2,PP3,PP5

Figure 3. Pathogenic variants detected in the *SERPINA1* gene through next-generation sequencing analysis.

AAT deficiency affects both sexes equally and is typically diagnosed in adults during the fifth decade of life (around ages 40-45)[5]. A comprehensive study evaluating the disease burden of AAT deficiency highlighted its significant pulmonary and hepatic morbidity. Beyond chronic obstructive pulmonary disease (COPD), emphysema, and bronchiectasis, patients with AAT deficiency may also present with panniculitis, HT, diabetes mellitus, cardiac disease, and pulmonary HT, underlining the substantial impact of the condition on both patients and healthcare systems[6,7]. Our patient was 78 years old and apart from HT, had no evidence of liver involvement or other comorbidities.

A recent study based on data from the European Alpha-1 Research Collaboration, a deep phenotyping registry supported by the European Respiratory Society, analyzed patients diagnosed with AAT deficiency and bronchiectasis[8]. Among 418 patients stratified by chest CT findings, 38 had only bronchiectasis, 190 had only emphysema, and 113 had both conditions. The average age was 55, the majority were female (53.3%), 41% had never smoked, and the mean FEV1 was 59%. Our patient shares similar characteristics with this cohort.

The two most common AAT deficiency mutations worldwide are PIS and PIZ (accounting for ~95% of cases); however, over 500 variants have been described. In our case, the rare PIM Palermo variant was identified. This mutation was first reported by Faber et al.[9] in 1994 as one of fifteen newly characterized AAT variants. They highlighted three rare variants PIQ0 Saarbruecken, PIQ0 Lisbon, and PIM Palermo as clinically significant due to their extremely low or undetectable serum AAT levels.

In 1997, Jardí et al.[10] detected the PIM Palermo mutation in six members across three generations of the same family; interestingly, none of these individuals had clinical evidence of lung disease. Karadoğan et al.[11], in their study conducted in Türkiye on the clinical implications of *SERPINA1* variants, reported serum AAT levels ranging between 0.2 and 0.9 g/L in individuals with the PIM Palermo mutation. They emphasized that MMalton, MNichinan, and MPalermo mutations were particularly associated with hepatic dysfunction and emphysema, especially in homozygous individuals. However, as their study focused on AAT deficiency and COPD, no specific data regarding the prevalence of bronchiectasis were provided.

Lepiorz et al.[12] reported bronchiectasis in a 51-year-old woman with the PIM Palermo mutation in the absence of COPD. Similarly, Feitosa et al.[13] categorized the PIM Palermo mutation as one of the variants that could lead to severe liver disease and extensive emphysema.

In conclusion, AAT deficiency is a known contributor to the development of bronchiectasis. While PIS and PIZ are the most commonly implicated mutations, studies specifically linking the PI*M Palermo mutation to bronchiectasis remain limited. This case contributes to the literature by highlighting the potential role of this rare mutation in the pathogenesis of bronchiectasis.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Author Contributions

Surgical and Medical Practices: C.D., G.S.Y., Concept: C.D., E.Y.G., Design: C.D., E.Y.G., Data Collection and/or Processing: B.Y., G.S.Y., Analysis or Interpretation: B.Y., E.Y.G., G.S.Y., Literature Search: B.Y., C.D., Writing: B.Y., C.D.

Conflict of Interest: The authors have no conflict of interest to declare.

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