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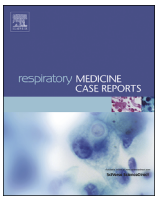

Case Report

A rare AAT variant presenting in a COPD patient: Q0 amersfoort mutation

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ABSTRACT

Introduction: Alpha-1 antitrypsin (AAT) deficiency, characterized by reduced synthesis of a serine protease inhibitor in liver cells, has been recognized to contribute to the development of emphysema and liver disease. Additional clinical manifestations encompassing respiratory disorders and dermatological issues have also been documented.

Case: A 56-year-old male patient presented with dyspnea. Despite being a non-smoker, he had a diagnosis of chronic obstructive pulmonary disease (COPD) five years ago. Utilizing inhaled corticosteroids (ICSs) - long-acting β2-agonists (LABAs)- long-acting muscarinic antagonists (LAMAs) inhalers, the patient's medical treatment had ceased for the past four months due to inhaler depletion. High-resolution thoracic computed tomography unveiled bilateral emphysematous regions, predominantly located in the lower pulmonary lobes. In light of the absence of smoking history, the suspicion of AAT deficiency was raised, prompting the assessment of serum AAT levels. Subsequent analysis indicated diminished AAT levels, prompting the collection of a dried blood sample for genetic evaluation. Genomic DNA amplification was performed using polymerase chain reaction (PCR), succeeded by allele-specific hybridization via Luminex XMAP Technology. This analysis disclosed a Q0amersfoort (Exon 2 Y160TAC > Ter TAG) (+/+) variant linked with AAT deficiency, originating from a frame-shift mutation that triggers a null (Q0amersfoort) stop codon.

Conclusion: The presentation of COPD-related emphysema in a non-smoker underscores the necessity to consider AAT deficiency in the differential diagnosis.

1. Introduction

Alpha-1 antitrypsin (AAT) is an antiprotease primarily produced by liver hepatocytes that inhibits the activity of several proteases including human neutrophil elastase, proteinase-3, and plasmin activator. The normal plasma concentration ranges from 120 to 200 mg/dL [1,2]. A plasma concentration below 11 μM (<50–80 mg/dl, depending on the assay) indicates AAT deficiency.

The prevalence of α1-antitrypsin deficiency (AATD) in the general population varies from 1:2000 to 1:5000 in some regions of Europe to 1:5000 to 1:10,000 in the United States and Canada. AAT deficiency arises from the inheritance of two alleles with severe deficiencies in the SERPINA-1 gene, located on the 14q31–32.3 chromosome segment. Normal alleles are referred to as PIM, with the PIM1-Val213 subtype being the most common in Europe and North America (44–49 %). The most common deficiency mutation causing very low serum AAT levels (10–15 % of normal) is the Z mutation (p.Glu366Lys) [3,4]. The S mutation (p.Glu288Val) is associated with mildly reduced AAT levels (30–40 % of normal). The most common deficiency alleles in populations of European descent

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are PIS and PIZ, with frequencies of 5–10 % and 1–3%, respectively. Approximately all clinical cases associated with AATD contain the PI*ZZ allele in a homozygous or compound heterozygous state. Despite being one of the most common genetic disorders among Caucasians, an estimated 90 % of individuals with severe AATD remain undiagnosed. Several rare null variants associated with plasma AAT levels of less than 1 % (referred to as Q0) have been identified, resulting from various molecular mechanisms. Frameshift or nonsense mutations lead to unstable mRNA or truncated/unstable proteins (e.g., Q0amersfoort) [5]. Other mechanisms include complete gene deletions (e.g., Q0 Isola di Procidą) or insertion mutations (e.g, Q0 Madrid). Hundreds of variants of the SERPINA1 gene have been identified through molecular analysis, with about 70 of them being associated with clinical symptoms.

Imbalance in protease-antiprotease due to AAT deficiency leads to alveolar wall damage, resulting in conditions such as emphysema and chronic bronchitis [6]. Early-onset "pure" panacinar emphysema can lead to classic respiratory diseases in adulthood, such as chronic obstructive pulmonary disease (COPD) and asthma, or manifest as bronchiectasis. Other pulmonary symptoms, such as airway hyperreactivity, wheezing, chronic cough, and sputum production, have also been described. The prevalence of COPD patients with AAT genetic deficiency, including all mutations, is 10 %, prompting the World Health Organization (WH0) to recommend screening for AATD at least once during the lifetime of all COPD patients [7].

In this case, we present a rare AAT genetic mutation case in a COPD patient presenting with severe shortness of breath and classic emphysema. Interestingly, the patient carried the rare Q0amersfoort mutation in a homozygous form, which is an insertion of cytosine and adenine (CA) in exon 2.

2. Case presentation

A 56-year-old male patient of Turkish origin presented to the emergency department with severe shortness of breath over the past few days. He had not received medical treatment for the past 4 months. He had never smoked and had a known additional condition of hypothyroidism. He was diagnosed with COPD 5 years ago, and there was no family history of respiratory or liver disease. There was no history of childhood asthma or allergies. His occupation was found to be a welding master. He had not had any emergency admissions for the past two years. His first laboratory workup showed leukocytosis at 10.18 g/L (normal range: 4–10 g/L), slightly elevated C-reactive protein at 14 mg/L (normal range: <5 mg/L), and a platelet count of 281 $\times$ 10^3/μL (normal range: 150-450 $\times$ 10^3/μL). eosinophils were at 1 % (normal: <4 %). Bronchiectasis study, including IgA, IgM, IgG, and subclasses, was normal. Nuclear antigen screening (ANA, RNP/Sm, Sm, SS-A, SS-B, Scl70, CentB, Ho-1, Rib-P) was normal. Antineutrophil cytoplasmic antibody (ANCA) test was negative. Interferon gamma release test for specific T-cell response to tuberculosis antigen was negative.

Echocardiography showed normal right and left heart functions, and brain natriuretic peptide (BNP) levels were normal.

Liver function tests revealed ALT 10 U/L, AST 11 U/L, GGT 18 U/L, and total bilirubin at 0.51 mg/dl (indirect bilirubin: 0.31 mg/dl). Abdominal ultrasonography showed normal liver size, smooth contours, homogeneous parenchyma, and no pathological findings.

High-resolution computed tomography (HRCT) revealed widespread emphysematous changes in both lungs, predominantly in the lower lobes. An atelectatic appearance was observed in the left lung. There were no new nodular formations compared to the patient's high-resolution thoracic computed tomography in 2020 [Fig. 1].

Respiratory function test report showed a forced expiratory volume in 1 second (FEV 1) of 0.99 (31 % predicted), and a FEV 1/forced vital capacity (FVC) ratio of 55.70 (71 % predicted).

The patient's serum AAT level was below 0.16 g/L (measured using the Cobas C702 nephelometry kit, Roche, Basel, Switzerland; quantification range; 0.9–2 g/L, detection limit 16 g/L). Genetic testing was performed on the patient with severe congenital alpha-1 proteinase deficiency. A mutation in exon 2 of SERPINA-1 gene causing a homozygous stop codon [Tyr(160)→stop] was identified.

It was decided to start 60mg/kg/1 $\times$ 5 intravenous AAT 1000MG in 83 kg patients with a genetic mutation and an FEV1 value of 31 % as a result of the pulmonary function test. No decrease in FEV1 value was observed in the 1-year follow-up, no COPD attack was experienced.

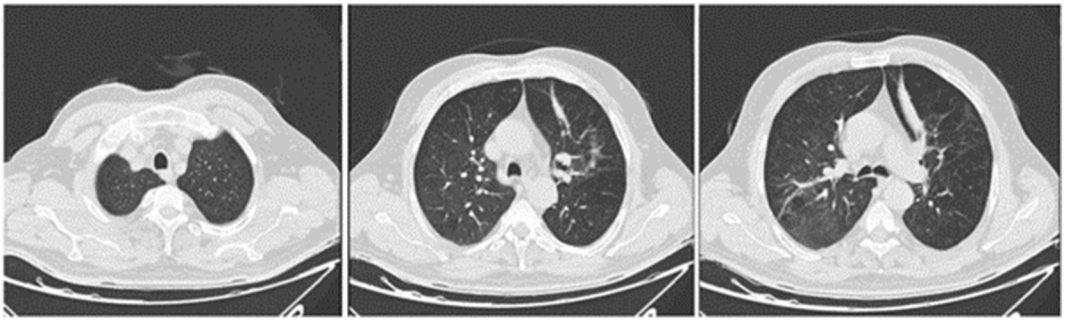

Fig. 1. In computed tomography (CT) of the thorax, Images show widespread emphysematous areas.

3. Discussion

The development of chronic obstructive pulmonary disease (COPD) can be attributed to risk factors such as harmful dust and particles, smoking, and occupational exposures, as well as genetic factors such as AAT deficiency. Genetically susceptible individuals exposed to environmental risk factors for a prolonged period or at high doses can lead to chronic inflammation and the development of chronic bronchitis and/or emphysema. AAT deficiency is classically associated with panacinar pulmonary emphysema, a genetic disease that is clinically underdiagnosed. Although less common, an association between AAT deficiency and bronchiectasis has also been described, and testing for AAT deficiency is recommended in the evaluation of bronchiectasis [2,8,9].

Thus far, over 100 different alleles have been identified, each representing a distinct phenotypic variant of the AAT glycoprotein [10]. Normal alleles are denoted as M alleles and are associated with normal serum plasma levels of AAT. Deficiency alleles, including the Z and S variants, are associated with <20 μmol/L serum plasma levels of AAT. Null alleles, like Q0, result in undetectable levels of AAT and are very rare mutations. The Q0amersfoort allele, as a severe AAT deficiency mutation, is characterized by an nonsense mutation leading to the formation of a stop codon. This allele is typically characterized by very low AAT levels and leads to a null phenotype (PI Q0/Q0) [11]. While different AAT alleles were traditionally characterized by isoelectric focusing, which remains the gold standard for phenotypic analysis in experienced reference laboratories, whole-genome sequencing and genotyping are now widely available [10]. As recommended by the current diagnostic algorithm, we utilized a combination of nephelometry and whole-genome sequencing to quantify plasma AAT levels. Overall, it is assumed that null mutations are very rare. However, the prevalence of COPD associated with AAT deficiency, the lack of general awareness of AAT deficiency, and diagnostic strategies that bypass full gene sequencing may lead to an underestimation of the prevalence [12]. Interestingly, the mutation in this case was found in a homozygous form, indicating a hereditary mechanism. Although this mutation may have a local prevalence in the patient's region of origin (Turkey), this has not been investigated [12].

The potential for augmentation therapy with intravenous AAT for severe AAT deficiency was discussed. In Germany, treatment indication is severe AAT deficiency (<80 mg/dL) and an FEV1 between 35 % and 60 %, although this may vary in different countries. Replacement therapy has been shown to reduce the progression of emphysema when assessed by intermittent computed tomography [13]. The effectiveness in slowing the decline in lung function has been demonstrated through a meta-analysis that included controlled and uncontrolled trial data [14]. Some studies have suggested positive effects of replacement therapy on airway inflammation [15,16], although its effects on bronchiectasis have not been thoroughly investigated. Given the limited evidence for replacement therapy in cases, it was preferred in this case. Additionally, genetic testing was recommended for the patient's children [7].

4. Conclusion

The genetic cause of chronic obstructive pulmonary disease (COPD), AAT deficiency. Should not be overlooked in etiology, and serum AAT levels should be measured in every COPD patient. Particularly in countries along migration routes, the significant prevalence of rare mutations should not be underestimated. For the clinical and epidemiological significance of rare null mutations causing severe AAT deficiency, further controlled studies are needed.

CRediT authorship contribution statement

Seda Tural Önür: Writing – original draft. **Kardelen Karaca Şenkal:** Writing – original draft.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this case report. They affirm that they have no financial, professional, or personal relationships that could inappropriately influence or bias their work. This case report is solely the result of their independent research and clinical findings.

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