Case Report

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Novel mutation (M_{angera}-E288V) in alpha-1 antitrypsin deficiency

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ABSTRACT

Background: Alpha-1 antitrypsin deficiency is an autosomal, codominant disorder caused by mutations of the SERPINA1 gene. Several mutations have been described associated with the development of pulmonary and/or chronic liver diseases. We report a novel mutation M_{angera}, identified for the first time in an Italian patient originating from the city of Angera (Varese), Italy.

Case presentation: This case report describes a 64-year-old Italian male, a lifelong non-smoker, diagnosed with severe alpha-1 antitrypsin deficiency (AATD) as composed heterozygous with S allele and a novel mutation named M_{angera}. The patient presented with exertional dyspnea and had reduced serum AAT levels (0.54 g/L). Pulmonary function tests indicated mild airway obstruction with preserved diffusion capacity, and chest CT scans revealed early centrilobular emphysema and fibrotic changes. Genetic analysis was performed, finding a previously unreported mutation. Despite the severe AAT deficiency, the patient exhibited no significant clinical, radiological, or functional deterioration. Given the absence of disease progression, augmentation therapy was deferred in favor of ongoing annual monitoring.

Conclusions: This case report highlights the necessity of referring patients to specialized centers equipped with the expertise and tools required for precise diagnosis. Furthermore, the identification of the M_{angera} mutation expands the spectrum of known *SERPINA1* variants associated with severe AATD, emphasizing the ongoing need for vigilance and thorough investigation in cases of suspected deficiency.

Key words: alpha-1 antitrypsin deficiency, clinical manifestations, genotype, rare allele

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Introduction

Alpha-1 antitrypsin deficiency (AATD) is a rare, autosomal co-dominant disorder. The heterogeneity of clinical manifestations in AATD is related to the complexity of the biological functions of α1-antitrypsin (AAT), which contributes to its frequent underdiagnosis. AAT is a neutrophil elastase inhibitor (an antiprotease) encoded by the SERPINA1 gene, located on chromosome 14. Its primary function is to protect pulmonary tissue from protease-induced degradation. Most of AAT is synthesized by hepatocytes, from where it passively diffuses into the lungs via the bloodstream. The structure (and thus the functionality) of the protein, along with the circulating levels of AAT, are determined by the co-dominant expression of parental alleles [1-3]. To date, more than 500 variants of SERPINA1 gene have been identified, and new mutations continue to be discovered. These variants are named based on their electrophoretic mobility, denoted by a letter, and the city in which the index case was born [4, 5]. Mutations can be broadly classified into three categories: normal variants, with serum AAT levels comparable to those of the general population; deficient variants, with reduced but still detectable plasma AAT levels; and null variants, characterized by undetectable plasma AAT levels [6].

Guidelines [2, 3] recommend suspecting AATD in all patients with Chronic obstructive pulmonary disease (COPD), adult-onset asthma, bronchiectasis, unexplained liver manifestations, panniculitis, or ANCA-associated vasculitis. In such cases, the patient should undergo plasma AAT and C Reactive Protein (CRP) testing. If AAT levels are reduced in the presence of normal CRP values, second-level investigations are indicated [7]. These include molecular analyses performed in specialized centers, such as genotyping, phenotyping, and possibly gene sequencing to diagnose AATD and assess its severity. Family screening is recommended for first-degree relatives of individuals with at least one pathological allele [2, 3, 7].

Once diagnosed, augmentation therapy is indicated for patients with severe AAT deficiency who are over 18 years old, exhibit compatible pulmonary clinical manifestations (FEV_1 < 65% and/or an annual decline > 100 mL, pulmonary emphysema, and reduced or declining DL_{CO}), and are non-smokers or have quit smoking [2, 3].

In this case report, we describe a novel mutation, M_{angera}, identified for the first time in an Italian patient originating from the city of Angera (Varese), Italy; the patient carried also the S variant in heterozygosis. M_{angera} and S alleles are located on different homologous chromosomes, but at the same position (in trans).

Methods

Biochemical and genetic tests to diagnose AATD were performed at the Centre for Diagnosis of Inherited Alpha1-Antitrypsin Deficiency in Pavia (Italy) with the understanding and written consent of the subject. The samples underwent a diagnostic algorithm that comprises the determination of AAT and C-reactive protein serum levels, the phenotyping by IsoElectroFocusing (IEF) analysis, the genotyping for the detection of the 14 most common alleles by AAT genotyping test (Progenika) and SERPINA1 gene sequencing with Sanger method (Figure 1) [8-10]. Pathogenicity prediction programs (REVEL and Polyphen) were applied to understand the meaning of the new variant.

Case presentation

The patient is a 64-year-old Caucasian Italian man, who has never smoked and has a history of occupational exposure as a panel beater. He denies any drug allergies. He reports that his father died of laryngeal carcinoma and has no family history of respiratory diseases. His medical history includes arterial hypertension under pharmacological treatment, untreated Hashimoto's autoimmune thyroiditis, maculopathy in the left eye, psoriasis of the left knee.

At age 61, after experiencing several episodes of exertional dyspnea (mMRC2), he consulted his general practitioner, who recommended performing routine tests, including protein electrophoresis, which showed a reduced concentration of alpha-1 globulins. In light of this finding, he suggest to measure AAT levels. The test showed a reduced value of 0,54 g/L (normal

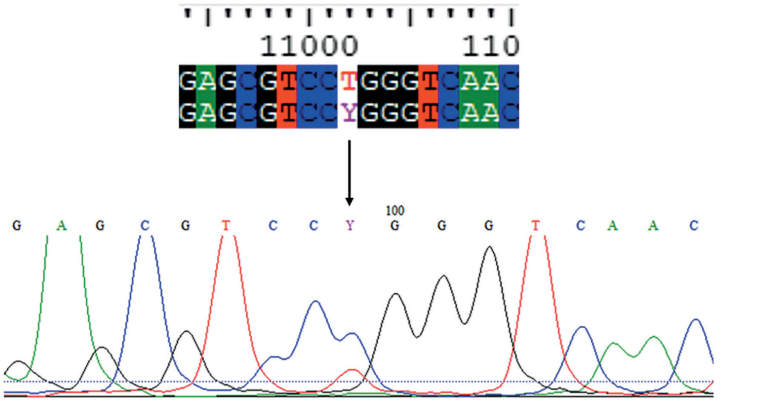

Figure 1. Electropherogram of M_{angera} (p.L327P-c.1553T>C) variant in heterozygosis.

Table 1. Spirometric values of patient since the diagnosi of AATD

Variables	September 2024			April 2025		
	Value	% on predicted	Z score	Value	% on predicted	Z score
FEV_1 (L/Sec)	3,64	103	+0,2	3,67	104	+0,25
FVC (L)	5,25	114	+0,9	5,14	112	+0,74
FEV_1/FVC, %	69		-1,00	70		-0,74
RV (L)	2,55	100	+0,21	2,85	112	+0,67
TLC (L)	7,85	108	+0,49	8,12	111	+0,79
RV/TLC, %	33,7		+0,06	35		+0,48
DL_{CO} (mmol/min*kPa)	8,67	94	-0,36	7,58	82	-1,1

range: 0,90–2,00 g/L). Due to this low result, a pulmonary consultation was advised, which recommended a full spirometry test and chest CT scan.

Spirometry showed dynamic and static lung volumes within normal limits, as well as DL_{CO} (Table 1). The chest CT scan showed early centrilobular emphysematous changes, a 4 mm fibrotic micronodule in the LID (Left Inferior Lobe) in the mantellar region, and thin fibrotic and/or hypoventilatory strands in the posterior costophrenic recesses.

Subsequently, referral was recommended to the Reference center at Pulmonology Unit at IRCCS San Matteo University Hospital in Pavia. In fact, 18 months after first pulmonary assessment, the patient underwent genetic testing, that identified two pathogenic alleles in trans: the S allele (p.E288V - c.863A>T rs17580) and a novel mutation named M_{angera}, after the town of the patient's birth. M_{angera} mutation consists on a point mutation at codon 327 in exon 4 (T>C transition), resulting in a substitution of Leucine (CTG) with Proline (CCG) (p.L327P -– c.1553T>C). Since protein phenotyping by IsoElectroFocusing did not reveal specific banding other than S and M, this variant was designated M_{angera}.

According to pathogenicity prediction programs [4], this mutation was classified as pathogenic; therefore, the final genotype indicates a severe Alpha-1 antitrypsin deficiency with a compound heterozygous profile: PI*S/M_{angera}.

The patient was then managed at our Reference center and re-evaluated few months after definitive diagnosis of AATD. On chest auscultation, vesicular

breath sounds were transmitted throughout all lung fields with no evident pathological sounds. Spirometry pre-bronchodilator (pre-BD) was repeated and showed stable dynamic and static volumes compared to previous results, DL_{CO} testing was within normal and stable limits (Table 1).

A high-resolution chest CT scan was performed, and the image was reviewed by our department, showing stability in the previously described findings. No progression of the emphysematous pattern or appearance of new abnormalities was observed.

A comprehensive blood tests work-up (Liver and kidney function, coagulation, blood count, Immunoglobulins) was performed and the results did not show any abnormalities. Autoimmunity (ANA, ENA, ANCA, IFI and Anti-M2) and Hepatitis serology were negatives.

The patient also underwent a complete abdominal ultrasound, which showed preserved morphology and homogeneous echotexture in liver, without any evident focal lesions. Some exophytic renal cystic formations were reported, for which referral to the general practitioner was made for potential urological evaluation.

A transient elastography (FibroScan) was also performed, showing a liver stiffness of 4.2 KPa, consistent with the absence of fibrosis.

The patient presents with a severe alpha-1 antitrypsin deficiency, without clear signs of disease involvement. In consideration of the absence of respiratory functional impairment, the stability of the radiological findings, and the patient's lack of symptoms, supplementation therapy was not initiated. It was decided to continue with an annual follow-up, currently ongoing, to determine the need and timing for the initiation of augmentation therapy, which the patient will be eligible for due to the severe deficiency, if there is a decline in respiratory function, the onset of related symptoms, or progression of parenchymal alterations.

Discussion and conclusion

The present study reports for the first time the M_{angera} mutation in an Italian patient with pulmonary manifestation.

This case report allows us to emphasize once again the importance of conducting genetic investigations through SERPINA1 gene analysis, as well as the need to refer these patients to specialized centers with the appropriate expertise and equipment to perform an accurate diagnosis. Effectively, without sequencing the new variant wouldn't have been identified and the patient would be mis-classified as an intermediate AATD subject. For this reason, the determination of AAT serum concentration is not conclusive, whereas our approach enables the complete identification and characterization of AATD and, where appropriate and indicated, the initiation of augmentation therapy. The effectiveness of replacement therapy is supported by numerous studies demonstrating its ability to improve patients' quality of life and slow the progression of the disease [11].

This case also serves as an example of the correct diagnostic pathway to follow in order to reach a complete diagnosis of AATD, with particular attention to the initial, non-specific symptoms (such as dyspnea and cough) in relation to the patient's clinical presentation. These signs prompted the local physician managing the patient to request a plasma AAT level test. Following the result, which showed reduced AAT levels, the patient was referred to a specialist who, after performing appropriate second-level investigations (spirometry and chest CT), correctly reference the patient to the Reference center, where a diagnosis of severe AAT deficiency was established.

Moreover, we furtherly expanded the panel of mutations associated with severe AATD, highlighting the importance of early diagnosis.

In conclusion, this case demonstrates how following the appropriate diagnostic pathway from the general practitioner, through the community pulmonologist, and ultimately to the specialized center, can lead to the timely diagnosis of a rare condition, allowing for both its study and the initiation of potential therapy at an early and effective stage.

List of abbreviations

AATD: Alpha-1 antitrypsin deficiency
AAT: Alpha-1 antitrypsin
COPD: Chronic obstructive pulmonary disease

CRP: C Reactive Protein
FEV_1: Forced Expiratory Volume in 1 second
FVC: Forced Vital Capacity
TLC: Total Lung Capacity
RV: Residual Volume
DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide
IEF: IsoElectricFocusing
CT: Computed Tomography
LID: Left Inferior Lobe
Pre-BD: Pre-bronchodilator
ANA: Antinuclear Antibodies
ENA: Extractable Nuclear Antigens
ANCA: Antineutrophil Cytoplasmic Antibodies
IFI: Indirect Immunofluorescence
Anti-M2: Anti-mitochondrial M2 antibodies

References

1. Ferrarotti I, Ottaviani S, De Silvestri A, Corsico AG. Update on α1-antitrypsin deficiency. Breathe (Sheff) 2018; 14: 17-24.
2. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003; 168: 818–900.
3. Miravitlles M, Dirksen A, Ferrarotti I, Koblizek V, Lange P, Mahadeva R, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in A1-antitrypsin deficiency. Eur Respir J 2017; 50: 1700610.
4. Giacopuzzi E, Laffranchi M, Berardelli R, Ravasio V, Ferrarotti I, Gooptu B, et al. Real-world clinical applicability of pathogenicity predictors assessed on SERPINA1 mutations in alpha-1-antitrypsin deficiency. Hum Mutat 2018;39: 1203–13.
5. Seixas S, Marques PI. Known Mutations at the Cause of Alpha-1 Antitrypsin Deficiency an Updated Overview of SERPINA1 Variation Spectrum. Appl Clin Genet 2021; 14: 173-94.
6. Ottaviani S, Barzon V, Buxens A, Gorrini M, Larruskain A, El Hamss R, et al. Molecular diagnosis of alpha1-antitrypsin deficiency: a new method based on Luminex technology. J Clin Lab Anal 2020; 34: 23279.
7. Balbi B, Benini F, Corda L, Corsico A, Ferrarotti I, Gatta N; on the behalf of IDA Group. An Italian expert consensus on the management of alpha1-antitrypsin deficiency: a comprehensive set of algorithms. Panminerva Med 2022; 64(2): 215-27.
8. Ferrarotti I, Scabini R, Campo I, Ottaviani S, Zorzetto M, Gorrini M, et al. Laboratory diagnosis of alpha1-antitrypsin deficiency. Transl Res 2007; 150: 267–74.
9. Ottaviani S, Gorrini M, Scabini R, Kadija Z, Paracchini E, Mariani F, et al. C reactive protein and alpha1-antitrypsin: relationship between levels and gene variants. Transl Res 2011; 157(6): 332–8.
10. Balderacchi AM, Barzon V, Ottaviani S, Corino A, Zorzetto M, Wencker M, et al. Comparison of different algorithms in laboratory diagnosis of alpha1-antitrypsin deficiency. Clin Chem Lab Med 2021; 59(8): 1384-91.
11. López-Campos JL, Carrasco Hernandez L, Caballero Eraso C. Implications of a change of paradigm in alpha1 antitrypsin deficiency augmentation therapy: from biochemical to clinical efficacy. J Clin Med 2020; 9(8): 2526.

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