Alpha-1 antitrypsin deficiency, SZ phenotype: a rare type of a rare disease. Case report

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Abstract

Alpha-1 antitrypsin deficiency is one of the genetic diseases with a clear impact on the structure and function of the lung, rarely diagnosed and treated. We present the case of a 51-year-old female patient, heavy smoker, known with chronic obstructive pulmonary disease (COPD) for 12 years, untreated, who was hospitalized for the first time in our clinic having symptoms of a severe COPD exacerbation. She has significant cardiac disease (rheumatic mitral disease, with previous episodes of pulmonary edema and cardiac arrest) and hepatitis B. The patient is hypoxic, with severe mixed ventilatory dysfunction. During the hospitalisation she received treatment of the exacerbation and after that she received recommendation of chronic inhaled bronchodilator and corticosteroid treatment. The test for alpha-1 antitrypsin deficiency has detected a plasma of 63 mg/dl, SZ phenotype. The patient returns for a second evaluation. Functional tests are significantly improved (despite inconsistent treatment) with the impressive improvement of FEV1 values and identification by plethysmography of a restrictive syndrome. Echocardiography identifies mitral valve changes likely rheumatic, severe pulmonary hypertension. Computer tomography was performed, highlighting discrete interstitial changes and denying the existence of emphysema. Marked increase in FEV1 values supported adding bronchial asthma to the list of diagnosis and recommendation to continue inhaled corticosteroid combination bronchodilator as treatment. The particularity of the case is the rare phenotype, association of asthma and COPD as the clinical manifestation and the presence of comorbidities, which complicates the diagnosis and prognosis.

Keywords: *alpha-1 antitrypsin deficiency, SZ phenotype, asthma - COPD overlap syndrome, asthma, COPD*

Rezumat

Deficitul de alfa-1 antitripsină, fenotip SZ: un tip rar de boală rară. Prezentare de caz

Deficitul de alfa-1 antitripsină este una dintre bolile genetice cu impact clar asupra structurii și funcției pulmonare, încă foarte rar diagnosticată și tratată. Prezentăm cazul unei paciente în vârstă de 51 de ani, mare fumătoare, cunoscută cu bronhopneumopatie obstructivă cronică (BPOC) de 12 ani, netratată, care se prezintă la o primă internare în clinica noastră acuzând simptomele unei exacerbări severe de BPOC. Este cunoscută cu patologie cardiacă semnificativă (boală mitrală reumatismală, cu episoade de edem pulmonar și stop cardiac în antecedente) și hepatită cu virus hepatitic B. Pacienta este hipoxemică, cu disfuncție ventilatorie mixtă severă. Pe parcursul internării a primit tratament al exacerbării și a primit recomandare de tratament cronic bronhodilatator și corticoid inhalator. Testarea pentru deficit de alfa-1 antitripsină a decelat o valoare plasmatică de 63 mg/dl și fenotip SZ. Pacienta revine pentru a doua evaluare. Funcțional este mult ameliorată (deși sub tratament inconstant), cu creșterea impresionantă a valorilor VEMS și identificarea prin pletismografie a unui sindrom restrictiv. Evaluarea ecocardiografică identifică modificări valvulare mitrale probabil reumatismale, hipertensiune pulmonară severă. S-a efectuat tomografie computerizată ce evidențiază discrete modificări interstițiale și infirmă existența emfizemului. Creșterea marcantă a valorilor VEMS au susținut adăugarea diagnosticului de astm bronșic și recomandarea de a continua tratament de asociere corticoid inhalator-bronhodilatator. Particularitatea cazului este reprezentată de fenotipul rar, asocierea astm - BPOC ca manifestare clinică, precum și prezența comorbidităților ce îngreunează diagnosticul și adumbresc prognosticul.

Cuvinte-cheie: *deficit de alfa-1 antitripsină, fenotip SZ, astm - COPD overlap syndrome, astm, BPOC*

Introduction

Alpha-1 antitrypsin (AAT) deficiency is a disease that can be held responsible for early aging of lungs and lung function impairment in young patients. Often times, however, in the case of patients with obvious risk factors and co-morbidities that overshadow the pulmonary manifestations, the diagnosis can be easily overlooked. The European Respiratory Society and American Thoracic Society (ERS/ATS) guidelines on diagnosis and management of alpha-1 antitrypsin deficiency recommend the examination of all chronic pulmonary obstructive disease (COPD) patients through both plasma level and genetic testing[1]. Despite this recommendation, for frequency reasons, GOLD guidelines recommend testing only COPD patients from areas with high prevalence of alpha-1 antitrypsin deficiency, pointing out that typical patients are young (under 45 years of age), with emphysema in the lower lobes[2]. However, the fact is that out of 19.3 million patients diagnosed with COPD, approximately 1.8 millions are estimated to be carriers of a modified PI (protein inhibitor) protein genotype, specific to AAT deficiency[3]. In Romania, genetic testing has become available starting 2012, through a partnership with the National Institute for Tuberculosis and Lung Diseases, Warsaw, Poland (Prof. Dr. Johanna Chorostowska-Wynimko), thus enabling the diagnosis of certain AAT deficiency cases.

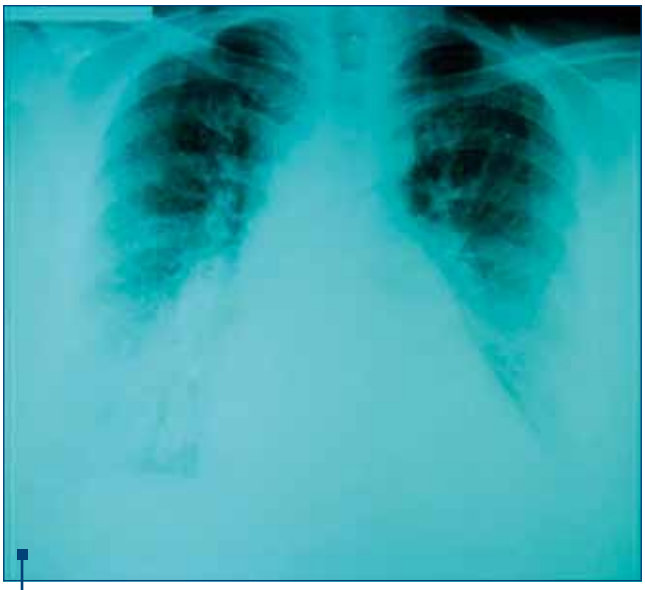

Figure 1. *Chest X-ray at first admission in clinic*

Case Report

First assessment

We present the case of a 51-year-old female, heavy smoker (about 35 pack-year), without occupational or environmental exposure to respiratory hazards, known with COPD (not documented) for approximately 12 years, under no specific treatment (because of socio-economic reasons), who was first admitted to our clinic with rest dyspnea, cough with abundant, purulent expectoration, symptoms that have occurred and worsened significantly over the past week. The patient is known to have significant heart pathology: severe mitral failure (probably rheumatic); atrial fibrillation with medium ventricular rate, treated with anticoagulants; severe pulmonary hypertension (identified as potentially chronic thromboembolic by the cardiologist), with two previous episodes of acute pulmonary edema and one episode of resuscitated cardio-respiratory arrest, as well as an episode of documented transient ischemic accident. She is also known to have chronic hepatitis B, ignored by the patient. She is now on the following treatment for her current condition: Zofenopril 30 mg/day, Digoxin 0.25 mg/day (a 2-day break/week), Spironolactone 50 mg/day, Furosemide 20 mg/day, Carvedilol 6.25 mg/day, isosorbide mononitrate 40 mg/day, Atorvastatin 40 mg/day and Acenocoumarol, regularly adjusted to the INR values. The existing recommendation (ignored) for her lung disease was an association of inhaled combination of Fluticasone 250 µg and Salmeterol 50 µg, 2 puffs /day.

The physical examination on admission revealed an afebrile patient, with affected general status, symmetrical vesicular murmur, with disseminated bronchial rales, oxygen saturation (SaO_2) was 91% while she was breathing ambient air, arrhythmic heart sounds, tachycardia (a heart rate of 92 beats/min.), split second heart sound, mitral systolic murmur 2/6, radiating in the armpit, no leg edema, no clear signs of deep venous thrombosis, liver palpable 1 cm below the costal margin, firm, sensitive, with rounded anterior edge, non-palpable spleen. The rest of the physical examination was normal.

The ***paraclinical investigations*** consisted of the following tests:

- Chest X-ray: decreased bilateral basal lung translucency, due to an accentuated reticulomicronodular pattern, with potential alveolar component (of condensation) added as well; very high cardiothoracic index because of the enlargement of both left and right cavities; enlarged pulmonary hili, with vascular appearance and linear hilar opacities towards the pulmonary parenchyma (Figure 1);
- Arterial blood gases upon admission: acute respiratory alkalosis (with polypnea) (pH=7.48, pCO_2=34mmHg, HCO_3^-=25mEq/L), with mild hypoxemia (pO_2=68mmHg);
- Electrocardiogram (ECG): atrial flutter with ventricular rate (VR) of 80/min. QRS axis =60 degrees, delayed transition (V4-V5), repolarization changes in the lateral area (figure 2A). Repeated ECG revealed fibrillo-flutter, with occurrence of a major left bundle branch block at high heart rates (a block also described in the previous discharge forms) (Figure 2B);
- Sputum smears and cultures came up negative for both non-specific bacteria and *Mycobacterium tuberculosis*;
- Blood tests (blood count, biochemistry) within the normal range; sub-therapeutic INR;
- Bronchoscopy performed on account of large quantities of bronchial secretion indicated abundant, adherent, purulent secretions that blocked the aspiration channel of the fiber bronchoscope. The investigation was prematurely interrupted because of patient's prolonged apnea;
- Spirometry, performed after clinical improvement, revealed a very severe mixed ventilatory dysfunction, with forced expiratory volume in the first second (FEV1) and vital capacity (VC) of approximately 24% of the predicted values and a Tiffeneau index (TI) of 69%.

The clinical and paraclinical investigations led to a diagnosis of COPD functional stage IV GOLD, group of risk D (considering the exacerbation that required hospital admission and a modified Medical Research Council Dyspnea scale – mMRC – of 3), exacerbated, with possible bronchiectasis (based on the medical history of abundant expectoration, as well as on the chest X-ray appearance). Considering the severe pulmonary dysfunction in a young patient, we decided to go through with the testing for alpha-1 antitrypsin deficiency. The evolution during hospitalization was favorable under antibiotic treatment (association of Cefoperazone with Sulbactamum, 2 grams twice a day), inhaled bronchodilators and corticosteroid (tiotropium bromide, 18 µg/day plus combination of Fluticasone 250 µg and Salmeterol 50 µg, 1 puff/ twice a day), with improved dyspnea, decrease in sputum quantity and purulence. The patient was discharged with the recommendation

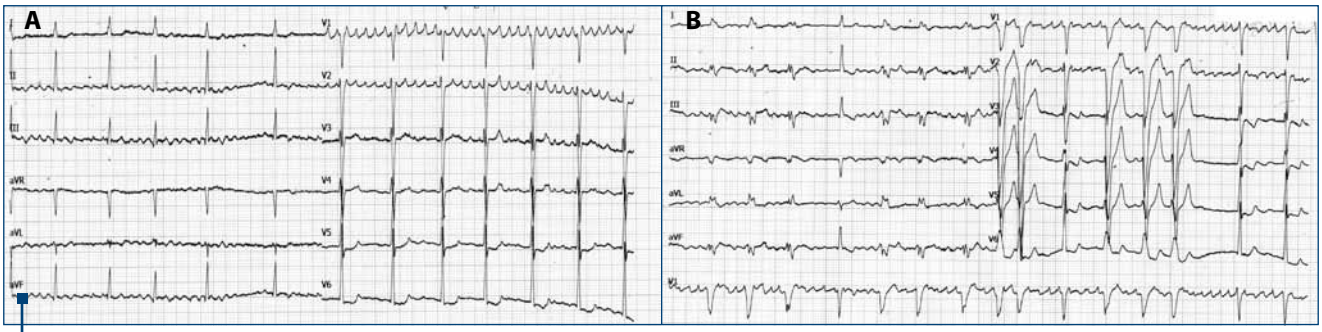

Figure 2. *ECG A: at first admission; B: later re-evaluation*

of continuing the long-acting anticholinergic bronchodilator therapy and the association of inhaled long-acting beta2-agonist bronchodilator - corticosteroid, as well as the cardiologic treatment.

Two months later, the results for the alpha-1 antitrypsin deficiency indicate a low AAT plasma level (63 mg/dl) and a SZ PI genotype, thus placing the patient at risk for both pulmonary disease (emphysema) and liver disease (cirrhosis)[4,5]. The patient was recalled for subsequent investigations.

Re-evaluation

Three months after the initial evaluation, the patient has dyspnea at medium-low exertion as only symptom. She stayed on the recommended inhaled therapy only for one month, then she abandoned the long-acting anticholinergic bronchodilator (for financial reasons), continuing to take (inconsistently) the association of inhaled long-acting beta2-agonist bronchodilator and corticosteroid. She still smokes, although she says she reduced the number of cigarettes per day. She had no other exacerbations in the meantime or other reasons for admission to the cardiology ward. After resuming the medical history, we identified two maternal aunts who died young from liver cirrhosis of unknown cause (possibly linked to the alpha-1 antitrypsin deficiency).

The physical examination is not different from the one at the first admission, the chest X-ray reveals no changes. Arterial blood gases show the same respiratory alkalosis, this time metabolically compensated, most likely in the context of polypnea (pH=7.45, pCO_2=30.9 mmHg, HCO_3-=21 mEq/L), with slight hypoxemia (pO_2=67 mmHg). At this admission, she has hepatic cytolysis with transaminases three times above normal limit. The viral hepatitis tests confirmed the infection with B hepatitis virus (positive surface antigen - HBsAg and HBc antibodies) and ruled out the possibility of a co-infection with C hepatitis virus (HCV) (negative HCV antibodies). Serum protein electrophoresis was normal.

In addition to the previous examination we performed a plethysmography with carbon monoxide diffusing capacity (DLCO), revealing a moderate to severe restrictive ventilatory dysfunction, with VC= 51% of the predicted value and lower total lung capacity (TLC) measured plethismographically; with DLCO moderately reduced and normal transfer constant (KCO), VC = 50.8% predicted, FEV1 = 48.3% predicted, TI = 80.81%, resistance in the large airways= 101.3% predicted, residual volume = 140.1% predicted, TLC plethysmographic = 3.54l (75.3% predicted), TLC-SB (single beath) = 2.75l (58.4% predicted), DLCO-SB = 44.5% predicted, KCO = 81.1% predicted. There was also a 560 ml increase in FEV1 from the previous admission, and also the lack of response to the bronchodilator in the current admission. The patient was constantly polypneic (also during the performance of the tests), which has possibly influenced test accuracy by underestimating the vital capacity. The 6-minute walk test was difficult to perform because of intense dyspnea during the test. The walked distance was 370 m (68% of the predicted distance), with a desaturation of 4 points during the effort (from SaO_2 of 96% to 92% at the end of the effort).

Given the restrictive pathology, we indicated a native chest computed tomography scan (CT scan), which revealed ground-glass pattern, with a predominantly basal location, significant cardiomegaly, right situated aortic arch and descending aorta, dilation of pulmonary artery (figures 3 A, B, C). No pulmonary emphysema detected.

The patient was reassessed from cardiologic point of view. Echocardiography showed dilated left cavities (left atrium = 49 mm, telediastolic left ventricle = 60 mm); modifications of the mitral valve with a high probability of rheumatic mitral disease, with restricted movement in the anterior mitral valve, "in dome", thickened cusps; maximum diastolic gradient = 19 mmHg, medium diastolic gradient = 6 mmHg (3^{rd} - 4^{th} degree regurgitation, large stenosis); moderate tricuspid regurgitation with a systolic pulmonary artery pressure (sPAP) estimated based on the tricuspid regurgitation jet of 73 mmHg (right ventricle - right atrium gradient of 63 mmHg, Figure 4) and dilation of the pulmonary artery trunk (41 mm at the ring).

Given the hepatic cytolysis, as well as the risk of liver impairment due to the alpha-1 antitrypsin deficiency, an abdominal ultrasound was performed (showing no significant changes) and also a gastroenterology consultation. The consult could not differentiate between the viral and the dystrophic cause of hepatic cytolysis in an AAT deficiency context, so it was recommended to perform the hepatitis B viremia levels and possibly hepatic fibrosis tests to set a specific treatment.

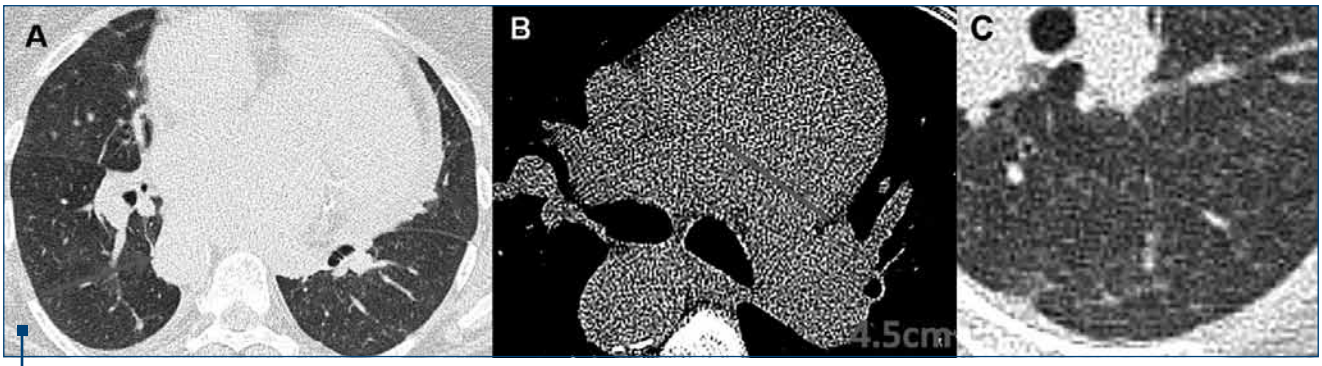

Figure 3. *Computed tomography images A: lower lungs, transversal section showing ground glass interstitial infiltration, important cardiomegaly, right situated descendent aorta; B: Great vessels transversal section showing pulmonary artery dilatation; C: Ground glass pattern in the lower left hemithorax*

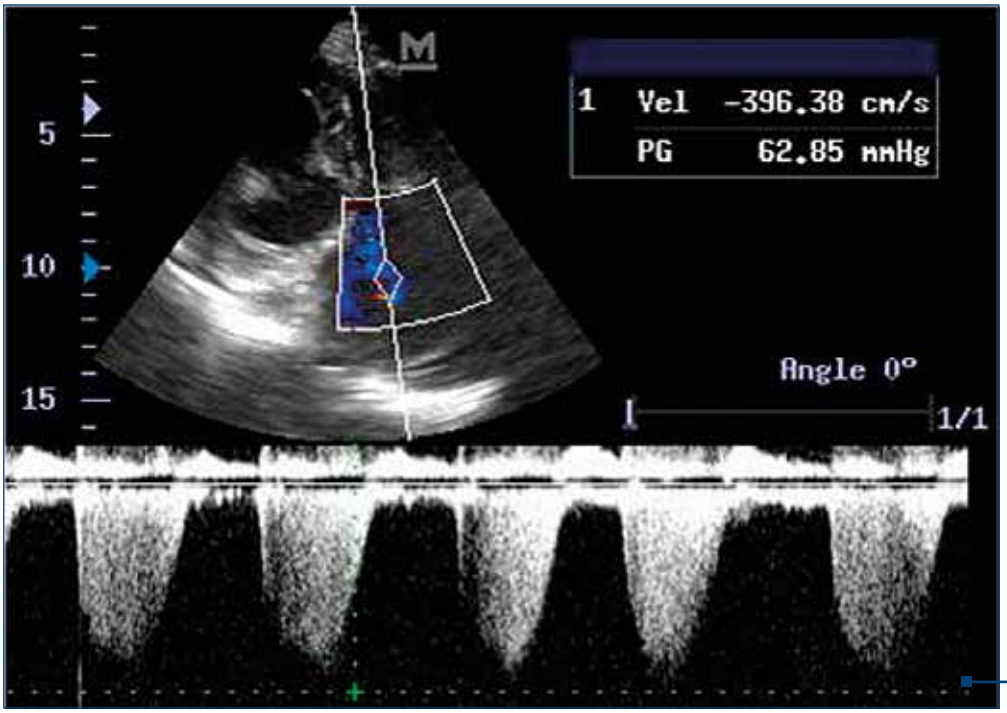

Figure 4. *Right ventricle - right atrium gradient calculation for estimation of sPAP*

Following this second set of tests, we ranked the pulmonary disease as COPD group D, stage II-III GOLD (CAT=33, mMRC=2, one known severe exacerbation – at the previous admission) associated with asthma (based on the significant increase of FEV1 between the two admissions, despite the negative bronchodilator test, and also on early onset of respiratory symptoms), alpha-1 antitrypsin deficiency – PI*SZ phenotype and severe pulmonary hypertension secondary to left heart disease. We recommended the continuation of treatment with inhaled combination of long-acting beta2-agonist and corticosteroid in the same dose (Fluticasone 250 µg/ Salmeterol 50 µg, one inhalation twice a day), the previously recommended cardiac treatment, vaccination against *influenza* and *pneumoccocus*; regular lung and heart re-evaluation and registration with the infectious disease clinic. The patient did not keep her appointment at the infectious disease clinic, and did not return for re-evaluations.

Discussion

1. Setting the diagnosis

If the initial diagnosis was COPD, severe exacerbation, based on the spirometry that demonstrated mixed ventilatory dysfunction, the second evaluation identified only restriction (confirmed by plethysmography), which does not confirm the initial diagnosis of airway obstruction due to COPD associated with restriction due to a possible pulmonary hyperinflation. On the contrary, the plethysmography and the alveolo-capilar transfer factor/DLCO revealed an interstitial pathology that associates a decrease in DLCO. In the absence of another pathology that could explain these particularities, we considered the restrictive ventilatory dysfunction to be a consequence of an advanced mitral disease. Severe heart failure can be responsible for fluid, protein and red blood cells extravasation in the alveolar space, leading in time to pulmonary fibrosis and thickening of the alveolar septum with the functional manifestation

of restriction with transfer factor alteration[6]. The more severe pulmonary hypertension can be responsible for the functional manifestations[7]. However, in the presence of risk factors (smoking, alpha-1 antitrypsin deficiency) and previous spirometry tests that revealed airway obstruction (with values clearly lower at that test), which was fixed during the current admission, we kept the COPD diagnosis that we re-staged according to GOLD guidelines. But we cannot ignore the significant functional improvement between the two admissions, with a 560 ml increase of FEV1 (87%) and the absence of airway obstruction at the second evaluation, under inhaled corticosteroid treatment, although inconsistent. These changes added to the early onset of the symptoms, support the diagnosis of bronchial asthma/ asthma, thus leaning towards the new asthma-COPD overlap syndrome according to the GOLD and GINA guidelines[2,8]. In this case, given the recommendations of the previously quoted guidelines and considering the good response to the associated therapy with inhaled long-acting beta2 agonist and corticotherapy, we chose this option to continue the treatment.

We also think that the CT scan appearance complements the above discussion, ruling out an intrinsic interstitial pathology and outlining discrete interstitial modifications, most likely in the context of the cardiac pathology. The CT scan also rules out the diagnosis of bronchiectasis, suspected at the first admission.

We believe that the pulmonary hypertension is caused rather by the significant mitral valvulopathy (a post-thromboembolic hypertension, as initially identified, cannot be excluded in the absence of a pulmonary arteriography or a tomography with contrast agent, but seems less likely in the existing clinical and paraclinical context). The association of both possibilities cannot be overruled.

In the current situation, the alpha-1 antitrypsin deficiency did not cause the emphysema, but was probably the risk factor who contributed to the development of COPD. Asthma is also a possible manifestation of alpha-1 antitrypsin deficiency[9], which is why the current guidelines recommend genetic testing in asthma patients with incomplete bronchodilator reversibility[1]. In these cases, especially in the case of smokers, distinguishing asthma with fixed obstruction from COPD can be difficult and the diagnosis of asthma-COPD overlap syndrome is preferred[8].

2. Indication for testing

If we consider patient's first hospital admission, the indication for AAT deficiency testing was COPD, especially since the diagnosis was already known (although without supporting documents) and the patient claimed she had early suggestive respiratory symptoms. Given the significant increase of the FEV1 value between the two visits and in the absence of airflow obstruction at the second evaluation, we would rather suggest a diagnosis of asthma, which would also be an indication for testing, but a less clear one. In the absence of the first evaluation, the indication is not at all firm. Neither COPD, nor asthma can be ascertained based only on the second evaluation (because of the lack of bronchial obstruction), plus the CT scan or the plethysmography did not show emphysema, most of the symptoms can be explained by the cardiac pathology, the hepatic disease could be caused by hepatitis B. Family history could also be a possible indication (the two aunts with unclear hepatic pathology, which might be a type B indication, according to the ATS/ERS guidelines - genetic testing should be considered and could be accepted or declined[1]). Therefore, in order to increase the diagnosis threshold for AAT deficiency, the focus should be on any detail regarding the personal, family or medical history and co-morbidities.

3. SZ phenotype

SZ is a rarely identified phenotype. This is due to both its rarity (less than 1/5,000 persons[10], due to the rare combination between alleles PI*Z and PI*S, with a frequency of less than 0.005 and below 0.02 respectively[11] in Romania, according to the estimates) and more attenuated symptoms than in the case of the PI*ZZ phenotype, which leads to preferential testing of severe PI*ZZ type cases. Thus, if we talk about index cases (symptomatic patients), 95% of the identified AAT deficiency cases are represented by phenotype PI*ZZ, 2% by PI*MZ, the remaining 3% including the other 30 phenotypes that can cause AAT deficiency (from the total of over 100 modifications of the PI gene)[12], including SZ.

The risk of developing COPD associated to the SZ phenotype is higher than in the general population (odds ratio for developing COPD is 3.26 in patients with the SZ phenotype compared to MM) according to a meta-analysis that covered 42 cases with SZ[13].

On the other hand, it seems that SZ phenotype displays manifestations that are different from the known ones. An imagistic study provided an example in this respect by outlining the lower frequency of emphysema in the SZ cases (42 cases) versus ZZ (63 cases), both for index cases (46% versus 91%, $p<0.001$) and for non-index cases (15% versus 61%, $p=0.011$), with prevalence of emphysema in apical areas in SZ (39%) versus ZZ cases (12%), $p=0.005$[14]. The same study revealed a higher share of cases without bronchial obstruction in the case of SZ (60%) versus ZZ cases (18%), $p<0.001$[14].

However, the scarcity of studies that include subjects with the SZ phenotype does not allow for clear conclusions, so, at the moment, SZ phenotype is not considered a separate sub-group of AAT deficiency patients.

Others: treatment, prognostic

The alpha-1 antitrypsin augmentation therapy is currently ascertained as the specific and efficient therapy that slows down the progression of the disease and the decline of FEV1, while improving the pulmonary emphysema[15,16,17]. However, it is an expensive therapy whose cost of almost USD 80,000/year[18] does not justify the widespread administration of the treatment. The ATS/ERS guidelines require a threshold AAT plasma level of 80 mg/dl, in the presence of a FEV1 between 30% and 65% or in a patient with an accelerated decline

of FEV1 (over 120 ml/year)[1]. Despite these recommendations, there are few countries that can afford and accept the augmentation therapy.

Starting from these considerations, even in a country with advanced therapeutic possibilities (which is not the case of Romania, unfortunately), the augmentation therapy could be controversial in the case of the presented patient (baseline FEV1 below 30%, subsequently 48.3%, but without obstruction or emphysema, cardiac co-morbidities that significantly impact the functional tests). In addition, active smoking and non-compliance to the recommended treatment (even for financial reasons) may be sufficient reasons for not recommending this therapy.

Consequently, we maintain the treatment of the underlying condition, starting with the cardiac pathology, continuing with the pulmonary pathology. The significant difference between the two admissions requires subsequent follow-ups to decide whether the inhaled treatment is necessary and what the optimum treatment should be. Given the asthma-COPD association, the inhaled corticosteroid is mandatory.

The prognosis of this patient is conditioned by her heart condition, especially since the patient has already developed significant cardiac episodes. This is compounded by the hepatic cirrhosis risk associated with both hepatitis B virus and PI*Z alleles[20] and, of course, by the pulmonary pathology (as the patient is not compliant to the inhaled treatment and continues to smoke, thus being exposed to a risk of accelerated decline of FEV1).

Testing first degree relatives for AAT deficiency should not be omitted either, according to the current recommendations[1]. Only one of the patient's two daughters was able to come for testing and she had the MZ phenotype and normal serum protein value.

4. Case particularity

The particularity of the case is given by the rare pathology it concealed (alpha-1 antitrypsin deficiency, phenotype SZ), the atypical manifestation of this pathology (asthma-COPD overlap syndrome), as well as the heart and liver co-morbidities, both impairing the diagnosis and making it difficult to define the case. ■

Special acknowledgements go to: Alina Arlet, MD (cardiology, "Marius Nasta" Institute), Svetlana Vasile Bugarin, MD (radiology and imagistic, "Marius Nasta" Institute), Lucian Negreanu, MD (gastroenterology, Emergency University Hospital of Bucharest), Cristina Teleaga, Chemist (Bronchoalveolar Lavage Laboratory, "Marius Nasta" Institute) for their contribution to this case.

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