Alpha-1-antitrypsin deficiency (AATD) and spontaneous pneumothorax: Guidelines do not recommend screening for AATD in patients with pneumothorax – What did we find in 10 years of clinical evidence?

Genetic influence on spontaneous pneumothoraces is supported by several lines of evidence: (1) pneumothorax can cluster in families – a family history of pneumothorax can be elicited in 10% of individuals presenting with spontaneous pneumothorax – familial spontaneous pneumothorax[1]; (2) mutations in the *FLCN* gene have been found in both familial and sporadic cases; and (3) pneumothorax is a known complication of several genetic syndromes.[2] These can be divided into three mechanistic classes: (1) those arising from mutations in tumour suppressor genes – Birt-Hogg-Dubé syndrome (BHDS), pulmonary lymphangioleiomyomatosis (LAM occurs both sporadically and in association with tuberous sclerosis complex – TSC); (2) connective tissue disorders – Marfan syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, homocystinuria, cutis laxa; and (3) those in which normal lung architecture is effaced – alpha-1-antitrypsin deficiency (AATD), cystic fibrosis and others.[2]

AATD is a genetic autosomal codominant disorder caused by mutations in *SERPINA1* gene.[3] It is one of the most prevalent genetic disorders, affecting 1/2000–5000 individuals, a similar or higher incidence than cystic fibrosis. However, it is an underdiagnosed condition.[4]

Alpha-1-antitrypsin (AAT) is the prototypic member of the serine protease inhibitor (SERPIN) superfamily of proteins and is mainly produced in the liver, reaching the lungs by diffusion from the circulation. AAT reacts with neutrophil elastase and provides over 90% of defense against the lower airway elastolytic load. In AATD, loss of the natural antiprotease screen against neutrophil elastase (and other proteases), as well as the loss of the anti-inflammatory effects of AAT, predisposes patients to emphysema.[5]

AATD primarily involves the lungs, liver and, less frequently, the skin. In the lung, AATD predisposes individuals to the premature onset of chronic obstructive pulmonary disease (COPD), with 1–2% of all cases estimated to be due to severe AATD.[3] The premature onset of panacinar emphysema is the most prevalent clinical correlate of AATD and the major cause of morbidity and mortality. Spontaneous pneumothorax may be the presenting manifestation of the disease or a complication of emphysema. Bronchiectasis has also been associated with severe AATD.[3]

Recommendations and guidelines of healthcare institutions, such as the World Health Organization, the Portuguese Society of Pneumology (SPP), the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the American and European Thoracic/Respiratory Societies (ATS/ERS), indicate that all COPD subjects and adults with nonreversible asthma should be tested for AATD at least once during their lifetime.[5] According to the Portuguese guidelines, screening should include an AAT serum level and, if it is <110 mg/dL, genotyping or phenotyping should be done.[3] As AAT behaves like an acute-phase protein, serum levels may be falsely augmented during inflammatory and infectious processes, so measurements should be done outside of acute episodes.

Current guidelines do not recommend screening for AATD in patients with pneumothorax, although this is a matter of controversy. Few studies have addressed this issue. Some support the measurement of AAT serum levels in patients with spontaneous pneumothorax while others failed to prove AAT deficiency was present in these patients.[6,7] A study published by Danielius Serapinas et al. revealed 7.7% of studied patients with spontaneous pneumothorax had AAT deficiency phenotypes including severe deficiency-related ZZ and SZ phenotypes.[8] Daniel and Teba reported spontaneous pneumothorax to be observed in patients with an abnormally low level of AAT.[9]

Our study was designed to evaluate the prevalence of AATD in patients with a first episode of primary spontaneous pneumothorax (PSP).

Clinical files of patients with a first episode of PSP admitted to Coimbra Hospital and University Centre between 2007 and 2017 were reviewed. Patients with an AAT serum level measurement were included in the study. Serum AAT levels were determined by nephelometry. In patients with low serum levels, phenotyping was done.

A total of 122 patients were admitted to our hospital with a first episode of PSP between 2007 and 2017, 103 of whom had an AAT serum level measurement and were included in the study. The mean age was 29.1 ± 12.8 years and 74.8% were males. Seventy-five patients had a chest CT done. Two (1.9%) patients had AAT <57 mg/dl, indicating severe deficiency. Genotyping was done in one patient that was found to be an SZ. The other patient was lost to follow up. Five (4.9%) additional patients had serum levels 57–110 mg/dl, indicating that an intermediate deficiency (heterozygosity) could be present. Genotyping was not done in any of these cases. Among the 7 patients with serum levels <110 mg/dL, only 3 patients were examined by chest computed tomography. One of them had no emphysema and another one had only subpleural blebs in chest CT, both of these had AAT levels between 57 and 110 mg/dl. Only the patient with severe AATD (genotype SZ), presented apical centrilobular and paraseptal emphysema.

In order to prevent or at least slow down the development of AATD related complications including the development of COPD and emphysema, early recognition of the disease is essential. Among patients with PSP we found 2 patients (1.9%) with severe AATD. This detection rate is similar to the detection rate of AATD in COPD patients (1–2%),[6] where screening is recommended, thus supporting the argument that patients with PSP should be routinely screened for AATD.

Additionally, we found 5 patients (4.9%) with AATD serum levels 57–110 mg/dL, some of which could have an intermediate deficiency, raising the detection rate of AATD in patients with PSP even higher.

Furthermore, as AAT is an acute-phase protein it may be elevated when pneumothorax occurs.[8] For that reason, there could be additional patients with an intermediate deficiency whose AATD levels were in the normal range during the episode of pneumothorax and so escaped detection in our study, once again making the detection rate higher. In order to solve this problem, we suggest that all patients

with PSP should have AAT serum levels measured outside the episode of pneumothorax or repeated later on.

Among the 103 patients included in the study, 75 were studied by chest CT. Current clinical guidelines do not recommend chest CT in first-time, unilateral spontaneous pneumothorax.[7,8] However, a recent study demonstrating the cost-effectiveness of CT to detect diffuse, cystic lung diseases in patients with first-time pneumothorax is among the reasons some authors argue for the adoption of this practice.[9] The presence of emphysema might raise the suspicion of AATD, like it did in our SZ patient.

In conclusion, our study supports screening of AATD in patients with primary spontaneous pneumothorax, as the detection rate was at least as high as in other conditions where screening is recommended.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Secondary pulmonary alveolar proteinosis in a patient with systemic lupus erythematosus

Dear Editor,

Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease and is pathogenetically classified into the following three types: autoimmune PAP, secondary PAP (sPAP), and congenital PAP.[1] sPAP is not associated with anti-granulocyte macrophage colony-stimulating factor (GM-CSF) antibody and accounts for 5–10% of PAP cases. sPAP is primarily caused by hematological disorders; sPAP caused by autoimmune diseases is extremely rare[2,3]; therefore, clinicians may not always consider the possibility of sPAP when abnormal findings on chest radiography and/or computed tomography (CT) are seen in patients with autoimmune diseases. We report here, a case of sPAP in a patient with systemic lupus erythematosus (SLE).

A 70-year-old woman presented to our hospital with a 1-month history of exertional dyspnea. She was a known case of SLE and had a 37-year-history of treatment with corticosteroids and immunosuppressive agents. Her respiratory sounds were normal, and she had no fever or cough; her oxygen saturation was 94% in room air. Chest radiography and computed tomography revealed diffuse ground-glass opacities in the lung fields bilaterally (Fig. 1A–C). Serum level of Krebs von den Lungen-6, a marker of interstitial pneumonia, was elevated (6416 U/mL); β-D-glucan and cytomegalovirus antigenemia were absent. Non-infectious acute interstitial pneumonia was suspected, and a high-dose corticosteroid was administered; however, radiographic findings and symptoms did not improve. Furthermore, multiple nodules with cavitation appeared in the lower lobe of the left lung. Bronchoscopy was performed; the bronchoalveolar lavage fluid (BALF) was markedly cloudy (Fig. 1D), and showed deposition of acidophilic granular material and foamy macrophages on microscopy. Additionally, *Nocardia* was detected in the nodules of the left lower lobe. Serum anti-GM-CSF antibody was absent. Finally, she was diagnosed with sPAP associated with SLE, and pulmonary nocardiosis. Early treatment of nocardiosis was necessary; therefore, antibiotics were administered, while the corticosteroid dose was tapered.