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Diffuse cystic lung disease as the primary tomographic manifestation of bronchiolitis: A case series

To the Editor,

The differential diagnosis of diffuse cystic lung diseases (DCLDs) includes a wide range of etiologies with different underlying pathophysiologic mechanisms.[1,2] Although morphological features, such as shape, distribution within the lung parenchyma and adjacent structures, and the presence of other pulmonary manifestations may suggest a specific underlying disease, a significant overlap exists between tomographic findings from different etiologies. In these cases, a lung biopsy may be required to establish a diagnosis.[1,2]

Lymphangioleiomyomatosis (LAM) is a rare slowly progressive neoplastic lung disease, which has a characteristic radiological appearance and affects mainly women of childbearing age. However, in women with regular and thin-walled cysts without extrapulmonary features compatible with LAM and with low levels of serum vascular endothelial growth factor D (VEGF-D), other potential rare etiologies may be included in the differential diagnosis, such as bronchiolitis, and smoking-related DCLDs.[3–5] We present the cases of eight women that were initially suspected with LAM whose histopathological analysis was compatible with bronchiolitis.

Among 347 patients with DCLDs followed at our center since 2006, eight (2.3%) had diffuse pulmonary cysts on HRCT and a histological diagnosis of cellular and constrictive bronchiolitis and were assessed in this study. Clinical, functional, tomographic, and histological features were analyzed. Written informed consent was obtained from all patients.

Pulmonary function tests adhered to recommended guidelines.[6–8] Computed tomography was performed in a supine position. Quantification of the volume of the cystic lesions was obtained automatically by densitovolumetry using a computer program (Advantage Workstation Thoracic VCAR software; GE Medical Systems, Milwaukee, WS, USA) and by selecting pixels between −1000 and −950 HU on soft tissue filter images. Paraffin blocks of lung tissue were retrieved for histological analysis (hematoxylin and eosin stain). Immunohistochemical staining for smooth muscle actin (SMA) and human melanoma black-45 (HMB-45) antibodies were examined.

Clinical and functional features at the time of lung biopsy are summarized in Table 1. All patients were non-smoking

Table 1 Demographic, clinical and functional characteristics (n = 8).

Female	8 (100%)
Age at diagnosis (years)	43 ± 14
Time between onset of symptoms and diagnosis (years)	2 ± 2
Current or former smokers	0
Environmental exposure	4 (50%)
Previous (mold and birds)	2 (25%)
Current (only birds)	2 (25%)
Clinical manifestations at diagnosis	
Dyspnea	6 (75%)
mMRC	1 (0–1)
Cough	4 (50%)
Wheezing	1 (12.5%)
Pneumothorax	1 (12.5%)
Pleuritic chest pain	2 (25%)
Xerostomy	2 (25%)
Xerophtalmia	1 (12.5%)
Skin lesions	0
SpO_2 on room air (%)	97 ± 2
Oxygen use	0
Pulmonary function tests	
FVC (L)	3.01 ± 0.73
FVC (%predicted)	88 ± 12
FEV_1 (L)	2.32 ± 0.85
FEV_1 (%predicted)	79 ± 23
FEV_1/FVC	0.73 ± 0.14
DLCO (mL/min/mmHg)	18.2 ± 4.6
DLCO (%predicted)	76 ± 17
Functional patterns	
Normal spirometry	5 (63%)
Obstructive	2 (25%)
Restrictive	1 (12%)
Air trapping[a]	2 (29%)
Reduced DLCO	3 (38%)
Positive response to BD[b]	1 (17%)

Values are expressed as mean ± SD, median (25th–75th percentiles) or n (%).
Definition of abbreviations: BD: bronchodilator; DLCO: carbon monoxide diffusing capacity; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; mMRC: modified medical research council dyspnea scale; SpO_2: oxyhaemoglobin saturation by pulse oximetry.
[a] Information available for 7 patients.
[b] Information available for 6 patients.

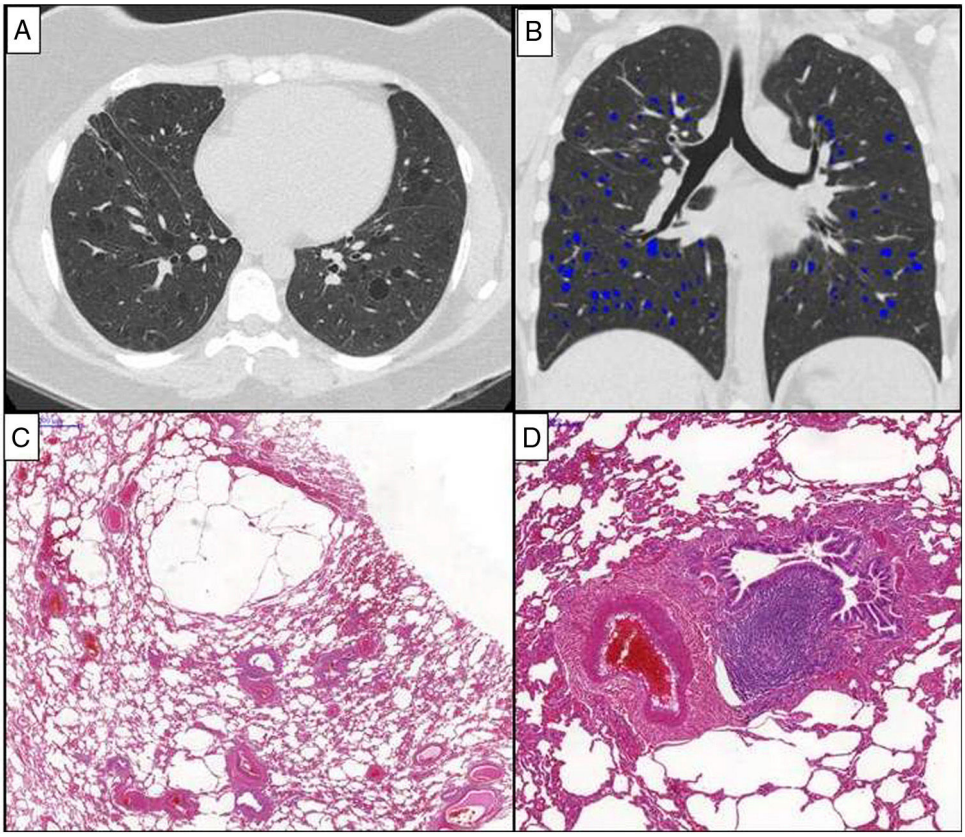

Figure 1 Chest HRCT scans (A and B) and histopathological findings (C and D) of a 38-year-old woman with chronic cellular bronchiolitis and diffuse cystic lung disease. (A) Axial CT image shows diffuse, regular, and thin-walled pulmonary cysts. The quantification of cystic lung lesions is depicted in blue (B). The percentage of the total lung area occupied with cysts is 2.75%. The photomicrographies (C and D) show mild inflammatory mononuclear cells infiltrating some of the bronchiolar walls. There are cystic alveolar changes in the nearby parenchyma tissue. Lymphoid follicles with reactive germinal centers are shown (hematoxylin and eosin stain) (D). Magnifications: C. $\times$13; D. $\times$70.

women with a mean age of 43 ± 14 years at diagnosis. The most common symptom was dyspnea (75%). Four patients had a relevant exposure history. No patient had any relevant personal or family medical history. Anti-Sjögren syndrome-related antigen A/Ro or B/La antibodies, the rheumatoid factor, and antinuclear antibodies were negative. Serum inflammatory markers, and immunoglobulins were unremarkable.

Mean FEV_1 and DLCO were $79 \pm 23\%$ predicted, and $76 \pm 17\%$ predicted, respectively. An obstructive pattern and reduced DLCO were found in 25% and 38% of patients, respectively.

All patients showed diffusely distributed multiple, regular thin-walled cysts on HRCT (Fig. 1). Other tomographic patterns were not found. Four patients underwent HRCT to investigate respiratory symptoms while in the remaining, pulmonary cysts were incidentally found during an investigation of abdominal pain or a routine exam of the chest. The median tomographic extent of cysts was 2.51% (interquartile 25%–75%: 0.8%–8.9%). Serum VEGF-D levels were available for only two patients (139 and 407 pg/mL).

All patients underwent a surgical lung biopsy. Histological analysis showed evidence of chronic cellular (Fig. 1) or constrictive bronchiolitis. Six cases had inflammatory mononuclear cells infiltrating the bronchiolar wall with a patchy distribution and variable intensity. Biopsies of two patients displayed infrequent, poorly formed and randomly distributed non-necrotizing granulomas. Two patients presented bronchiolar fibrosis. One patient had a discreet fibrotic thickening of the submucosa associated with luminal narrowing in some small airways, whereas another patient displayed complete focal obliteration of the bronchiolar lumen with fibrous scar formation. All patients presented with parenchymal cysts characterized by airspace distensions in the centrilobular and subpleural regions. The walls of these lesions contained residual alveolar tissue. Proliferation of immature smooth muscle-like cells was not detected.

DCLDs have a broad differential diagnosis. Clinical and tomographic findings combined with a multidisciplinary approach make differentiation of various entities possibile. In our study, we described eight women with DCLDs referred with an initial suspicion of LAM. Following a histopathological analysis they were diagnosed as having cellular or constrictive bronchiolitis, with mild severity, which is a very rare etiology for DCLD. Although suggestive, the tomo-

graphic patterns of the diffuse, regular and thin-walled cysts in women are not specific to LAM.[2,4,5] In the absence of definite findings, a pulmonary biopsy is mandatory to diagnose LAM.[3] Low availability of serum VEGF-D dosage is a limitation of our study.

Some findings on HRCT contribute to establishing the etiology of DCLDs. In pulmonary Langerhans histiocytosis, cysts are usually irregular, predominate in the upper and middle lung zones and may be associated with nodules.[1,2] In Birt-Hogg-Dubé (BHD) syndrome, cysts are multiple, thin-walled and predominantly basilar and paramediastinal.[1,2] Cysts in lymphocytic interstitial pneumonia occur in the lower lobes along the peribronchovascular bundle, frequently with ground-glass opacities.[2]

The typical pathological and immunohistochemical features of LAM were not identified in our study. Histologically, LAM nodules consist of two cellular subpopulations: the spindle cells express SMA and forms the core of the nodules surrounded by epithelioid cells that exhibit immunoreactivity for HMB-45 antibody.[9] On histopathology, the morphology of BHD cysts may resemble what was found in our cases. However, we excluded BHD based on clinical and tomographic features.[10] Cysts, emphysema, and respiratory bronchiolitis are identified in smoking-related DCLDs, but were not found in our study.[5] A combination of the DCLDs and small airway disease is mainly identified in specific conditions, such as Sjögren's syndrome, and it is thought that chronic small airway damage might lead to cyst formation in these patients. A possible explanation for the lung cyst formation in bronchiolitis is a check-valve obstruction with distal airspace overinflation related to air trapping, distal to the abnormal airways.[1,2]

In two cases, histological analysis showed evidence of chronic cellular bronchiolitis associated with infrequent, poorly formed, non-necrotizing granulomas, frequently seen in hypersensitivity pneumonitis (HP). Pulmonary cysts have been described in HP possibly due to partial bronchiolar obstruction.[2]

Potential etiologies for our patients with bronchiolitis include autoimmune disorders, such as Sjögren syndrome, post viral infections and HP. However, none of the etiologies raised were confirmed.

In summary, LAM is a prototypical DCLD with a characteristic appearance on HRCT. However, cystic features alone are inadequate to establish a diagnosis of LAM. In such context, bronchiolitis should be considered in the differential diagnosis of DCLDs.

Informed consent

Patients gave informed consent for this study.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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A rare case of pulmonary disease combining alpha-1-antitrypsin deficiency and common variable immunodeficiency

Dear Editor,

Alpha-1-antitrypsin (AAT) is a glycoprotein synthetized mainly by the liver, acting primarily in the lung as an inhibitor of neutrophil elastase, but also capable of regulating other proteases.[1,2]

Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder inherited in an autosomal codominant pattern, which is estimated to affect in Europe 1 in 2700 (Northern Europe) to 18,000 (Central Europe).[3–5] AATD increases the risk of chronic obstructive pulmonary disease (COPD), emphysema and chronic bronchitis, liver cirrhosis, panniculitis and c-ANCA (anti-neutrophil cytoplasmic antibodies) positive vasculitis, due to a proteolytic imbalance and/or negative effect of protein polymerization.[6]

Pathogenic mutations in *SERPINA1* gene (14q32.13) are the cause of AATD and whereas common M alleles are associated with normal concentrations in the serum, S and Z variants' have decreased circulating levels of AAT (60% and 15% of the normal values, respectively).[1] Most AATD cases are attributed to PI*ZZ genotypes (~95%) and the remaining ones to PI*SZ, PI*MZ, or any genotype combining rare deleterious mutations.[7] To date, there are more than 130 alleles described in the literature, most of them associated with a significant decrease in AAT circulating levels (deficiency variants) or leading to a total absence of protein (null alleles).[8,9] One of these variants is the PI*Mmalton (p.Phe52del in a M2 allele) that has been found to polymerize and to accumulate in the endoplasmic reticulum, being secreted into the bloodstream in less than 15% of normal AAT concentration.[1] Beside S and Z allele, p.Phe52del (PI*Mmalton or PI*Mpalermo if in a M1alele) appears to be the next most prevalent variant among AATD cases in Iberian Peninsula (54% in Spain and 40% in Portugal).[7–10]

On the other hand, common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by low serum concentration of immunoglobulins which may lead to assorted clinical features,[11] mainly recurrent bacterial infections of respiratory and gastrointestinal tracts.[12] CVID affects approximately 1 in 30,000 individuals and it is the second most common primary immunodeficiency in humans.[12] This disorder is highly heterogeneous and it basically encompasses a group of primary antibody failure syndromes that can be derived from distinct entities all causing some type of hypogammaglobulinemia. To date CVID diagnosis continues to be essentially done by different exclusion criteria.[13] Most cases are sporadic and thought to result from a complex interaction between environmental and genetic factors.[14] Still, in rare instances, CVID m is inherited in an autosomal recessive fashion, and in other rarer cases, the disease can be inherited in an autosomal dominant pattern.[14] Nevertheless, even when CVID is associated with a genetic mutation, additional environmental and genetic risk factors are likely to be necessary for disease onset.[14]

The advent of clinical manifestations and the detection of low levels of immunoglobulins may occur at any age from early childhood to old age.[13] In an European study, 34% of patients presented the disease before the age of 10 years, with male predominance of 2:1 before age 11, and a slight female predominance of 1.3:1 after the age of 30.[13]

So far, only two cases of subjects combining AATD and CVID have been reported.[15,16] Nevertheless, Sansom et al., while studying 43 patients with CVID found five patients with both conditions, suggesting a cumulative effect of AATD and CVID in the presentation of bronchiectasis.[17] In these reports, various A1AT genotypes were evaluated, including various combinations of Z with S and M alleles. Concerning the loss of lung parenchyma few studies have attempted to investigate the impact of sharing these respiratory illnesses. Still a previous work proposed a physical correlation between hypogammaglobulinemia and AATD, later confirmed by another study proving the occurrence of genetic linkage between immunoglobulin heavy constant gamma (Gm markers) loci (*IGHG1-3* genes) and AAT gene (*SERPINA1*).[15]

We present the case of a Portuguese woman, born in Coimbra (Central Portugal) and currently living in Madeira, with history of childhood asthma whose symptoms ceased spontaneously during adolescence. At the age of 32 and having been a tobacco smoker for a decade, the patient was hospitalized for pneumonia with a pleural effusion. Afterwards, respiratory symptoms, such as dyspnea and cough with sputum production become recurrent and multiple respiratory infections were diagnosed within a short time period (five years). In 2000, the patient was found to have CVID upon evaluation of immunoglobulins levels by nephelometry. Consequently, she initiated replacement therapy with subcutaneous immunoglobulin (so currently under 19 years of therapy).

At the age of 57, she was tested for AATD. This analysis showed that she had reduced AAT levels in the blood (18.7 mg/dL by nephelometry) and the initial genetic screening yielded a MM result. Given that the first genetic