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Clinical Report

Pulmonary Amyloidosis as a Differential Diagnosis in Interstitial Lung Diseases

Amiloidosis pulmonar como diagnóstico diferencial en las enfermedades pulmonares intersticiales

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ABSTRACT

Pulmonary amyloidosis is an uncommon condition that can mimic interstitial lung diseases (ILDs), leading to diagnostic delays. We describe two cases of diffuse alveoloseptal amyloidosis initially misdiagnosed as ILD. The first involved a 47-year-old woman with systemic AL amyloidosis, successfully treated with CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone) and autologous stem cell transplantation. The second case was a 72-year-old man with localized pulmonary amyloidosis, managed empirically with azathioprine and prednisone, showing slow progression but clinical stability. Histological confirmation using Congo red staining and immunohistochemistry was essential for diagnosis, and systemic disease was excluded through a comprehensive workup. These cases highlight the importance of considering pulmonary amyloidosis in the differential diagnosis of ILDs, especially in patients with unexplained interstitial patterns and monoclonal gammopathy. A multidisciplinary approach is crucial to avoid inappropriate treatment and ensure timely management.

Diffuse interstitial lung diseases (ILDs) constitute a heterogeneous group of clinicopathological entities characterized by similar clinical manifestations and diffuse involvement of the pulmonary parenchyma.[1] Their diagnosis is complex due to the existence of more than 150 recognized causes. Amyloidosis is an uncommon condition that can present with an interstitial lung pattern, a condition caused by extracellular deposition of misfolded, insoluble proteins that impair organ function.[2]

Pulmonary amyloidosis is relatively common histologically but rarely symptomatic. It can manifest in three forms: nodular, tracheobronchial, or diffuse alveoloseptal, the latter being the variant associated with interstitial lung disease (ILD). This form is particularly rare, with an estimated incidence of 1–3 cases per million person-years,[3] and its diagnosis and management pose significant clinical challenges.

We present two cases of diffuse pulmonary amyloidosis initially misdiagnosed as ILD. The first case involves a 47-year-old woman, non-smoker, presenting with dyspnea. Imaging revealed bilateral interstitial infiltrates with alveolar consolidation and mediastinal lymphadenopathy (Fig. 1a). PET-CT showed hypometabolic lymph nodes. Bronchoalveolar lavage and immunological tests were non-diagnostic. Lung function showed moderate restrictive pattern. Histological analysis of a tissue biopsy obtained by mediastinoscopy revealed amyloid deposits. Hematologic workup identified an IgG lambda monoclonal gammopathy with elevated lambda free light chains. Cardiac involvement was ruled out by electrocardiogram and echocardiography. This case was classified as systemic AL amyloidosis due to the presence of monoclonal gammopathy and multisystemic features. Treatment was initiated with the CyBorD regimen (Cyclophosphamide, Bortezomib, Dexamethasone), achieving partial response, followed by autologous stem cell transplantation.

The second case was a 72-year-old man, ex-smoker with chronic lumbar pain, whose chest X-ray showed bilateral interstitial changes (Fig. 1b). Transbronchial biopsy demonstrated

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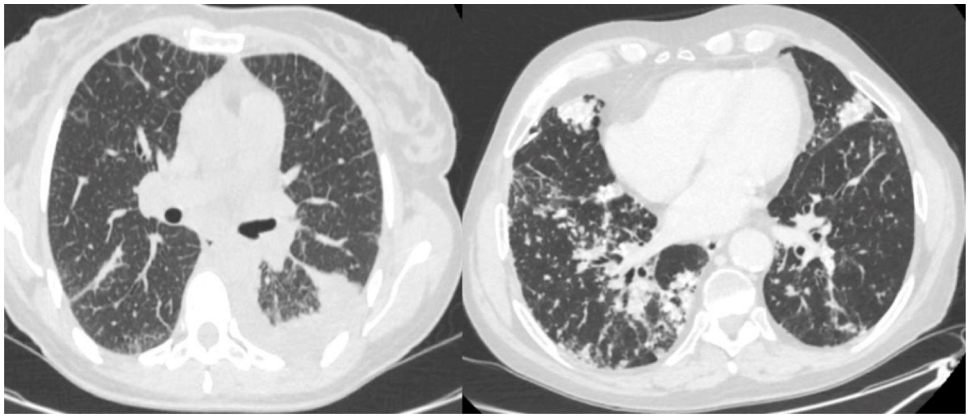

Fig. 1. On the left (a), computed tomography from the first case showing diffuse bilateral septal interstitial infiltrates with extensive alveolar consolidation in the left lower lobe and lingula. On the right (b), computed tomography from the second case showing bilateral infiltrates.

congo red-positive birefringent material. Surgical lung biopsy via video-assisted thoracoscopic surgery (VATS) was performed to obtain lung tissue, confirming the diagnosis. Systemic involvement was excluded through fat pad and bone marrow biopsies and normal laboratory tests and cardiac involvement was ruled out by electrocardiogram and echocardiography. This case was classified as localized pulmonary amyloidosis after exclusion of systemic involvement. Given radiological progression, the patient was treated with azathioprine and low-dose prednisone, showing slow radiographic and functional decline while remaining clinically stable.

Pulmonary involvement occurs in approximately 50% of patients with amyloidosis, predominantly in the AL subtype.[4,5] In alveoloseptal amyloidosis, the deposition of light chains within the alveolar septa alters lung structure and can radiologically mimic patterns seen in usual interstitial pneumonia (UIP), connective tissue disease-associated ILDs, and lymphangitic carcinomatosis. Histologic confirmation is essential to avoid misdiagnosis and inappropriate therapy.

The definitive diagnosis of amyloidosis requires Congo red staining and characteristic apple-green birefringence under polarized light. Subtyping can be done using immunohistochemistry or mass spectrometry. In both cases presented, amyloid subtyping was performed by immunohistochemistry, confirming AL-type deposits. Although a single organ biopsy confirming amyloid deposits is sufficient for diagnosis, in cases of diagnostic uncertainty additional biopsies may be required.

Assessment of pulmonary amyloidosis mandates exclusion of systemic disease with a thorough workup, including serum and urine immunofixation electrophoresis, free light chain assays, and biopsies of fat, bone marrow, and rectal mucosa. Differential diagnoses must include idiopathic interstitial pneumonias, neoplasms, and autoimmune conditions.

Treatment is tailored to the clinical form: systemic AL amyloidosis typically requires chemotherapy and/or autologous transplantation, whereas localized disease may be managed symptomatically or with surgical resection. Immunosuppressive therapy may be considered in cases with extensive pulmonary involvement. Although our patient was treated with CyBorD according to the protocols available at that time, current standard of care for systemic AL amyloidosis includes daratumumab-CyBorD, as supported by the ANDROMEDA trial and subsequent regulatory approvals.[6] The use of azathioprine and low-dose prednisone in the other case was an empirical therapeutic decision, given the absence of established treatments for localized pulmonary amyloidosis and the radiological progression observed.

In conclusion, pulmonary amyloidosis is a rare and often underrecognized cause of interstitial lung disease. Histological confirmation is indispensable for correct diagnosis and management. A multidisciplinary approach is essential to ensure optimal treatment and avoid diagnostic delays in this challenging subset of ILD patients. Pulmonary amyloidosis should be systematically considered in the diagnostic algorithm of ILDs, particularly in patients with unexplained interstitial patterns and monoclonal gammopathies.

Artificial intelligence involvement

The article has not been partially or totally produced with the help of any artificial intelligence software or tool.

Informed consent

Informed consent has been obtained from the patient for the publication of their clinical data and images.

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Authors' contributions

All authors have contributed to the drafting, supervision, and critical revision of the manuscript, and have approved its final version for submission.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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