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Case Report

Pulmonary amyloidosis as the presenting finding in a patient with multiple myeloma

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ABSTRACT

We present the case of a 58-year-old man who presented with dyspnea, cough, and weight loss and was ultimately diagnosed with pulmonary amyloidosis and multiple myeloma. Diagnosis was achieved with a lung biopsy which showed AL amyloid deposits involving the interstitium, vessels, and airway. He was treated with cyclophosphamide, bortezomib, and dexamethasone but died prior to completing treatment. His case is unique for the amyloid deposition found in all three lung compartments with clear pathophysiologic manifestations of each compartment, and the rapid disease progression that led to respiratory failure and death.

1. Introduction

Light chain (AL) amyloidosis is a type of systemic amyloidosis caused by deposition of monoclonal light chain fragments, and may occur in the setting of a plasma cell dyscrasia such as multiple myeloma [1]. Pulmonary involvement occurs in approximately 50% of amyloidosis cases, but pulmonary amyloidosis is a rare manifestation of multiple myeloma [2]. Pulmonary amyloidosis is typically characterized by one of three histopathologic patterns: nodular, diffuse alveolar-septal, and tracheobronchial [3]. These patterns are reflected by a host of pathophysiologic manifestations which can involve any lung compartment (airway, interstitium, vasculature), although most frequently only one or two compartments are seen to be affected [4]. Here, we describe a case of multiple myeloma and AL amyloidosis that initially presented with marked pulmonary symptoms and physiology due to diffuse pulmonary parenchymal and vascular amyloid deposition.

2. Case presentation

A 58-year-old Brazilian man with hypertension, dialysis-dependent renal disease, and recurrent deep vein thromboses due to congenital absence of the infrarenal inferior vena cava presented with six months of progressive exertional dyspnea, nonproductive cough, fatigue, and weight loss. He had adhered to thrice weekly dialysis sessions after developing end-stage renal disease one year prior, presumed to have resulted from acute tubular injury during a period of critical illness stemming from necrotizing fasciitis and influenza. He had no antecedent heart or lung disease and never smoked cigarettes.

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On admission, lung auscultation revealed bibasilar inspiratory crackles and prolonged expiratory phase. He required 2–4L/min supplemental oxygen via nasal cannula to achieve SpO₂ 90%. Labs were notable for hemoglobin 10.9 g/dL, NT-pro-BNP 12,139 pg/mL, calcium 9.7 mg/dL, CRP 102.4 mg/L, and negative testing for SARS-CoV-2 infection. On hospital day 3, chest CT showed diffuse ground glass opacities with peripheral nodularity, mosaic attenuation, and hilar and mediastinal lymphadenopathy. Fluid removal with dialysis did not improve his hypoxemia. Right heart catheterization demonstrated the following: right atrial pressure 3 mmHg, pulmonary artery pressure 51/20 mmHg (mean 32), and pulmonary capillary wedge pressure 5 mmHg. Subsequent high-resolution chest CT on hospital day 17 showed progressive diffuse ground-glass infiltrates with mosaic attenuation exaggerated on expiratory phases (Fig. 1, panels A–D). Pulmonary function testing revealed an FEV₁ 49% of predicted, FVC 55% of predicted, TLC 53% of predicted, RV/TLC 129% of predicted, and DLCO 22% of predicted. On hospital day 18, the patient underwent diagnostic VATS with 3 wedge resections. Hematoxylin and eosin (H&E) stains revealed diffuse parenchymal and vascular amyloid deposition as highlighted by Congo Red staining with apple green birefringence when viewed under polarized light (Fig. 2, panels A–D). Serum protein electrophoresis demonstrated elevated free lambda at 5309 mg/L with a free kappa/lambda ratio of 0.01. A subsequent bone marrow biopsy on hospital day 25 demonstrated a lambda-restricted plasma cell neoplasm, with plasma cells comprising 15–20% of the bone marrow cellularity. The pulmonary amyloid was confirmed to be AL (lambda)-type via liquid chromatography tandem mass spectrometry amyloid testing. Cardiac MRI demonstrated normal left ventricular wall thickness and no evidence of cardiac amyloidosis although sensitivity was limited by lack of gadolinium contrast.

On hospital day 27, he commenced treatment with cyclophosphamide, bortezomib, and dexamethasone (CyBorD). The patient completed 2 cycles but subsequently became acutely ill and was unable to complete his third cycle. He ultimately expired 6 months after the initial diagnosis as a result of progressive hypoxemic respiratory failure felt to be secondary to amyloid progression with superimposed bacterial infection.

3. Discussion

Although pulmonary involvement in systemic amyloidoses is relatively common, progressive subacute dyspnea and hypoxemia, as seen in this case, are rare as the primary presenting symptoms. Often, the diagnosis of pulmonary amyloidosis is made at autopsy in patients who otherwise did not exhibit respiratory symptoms [5]. The uniquely severe clinical presentation of this patient is likely explained by the unusual diffuse tricompartmental nature of amyloid involvement. Other possibilities such as concomitant

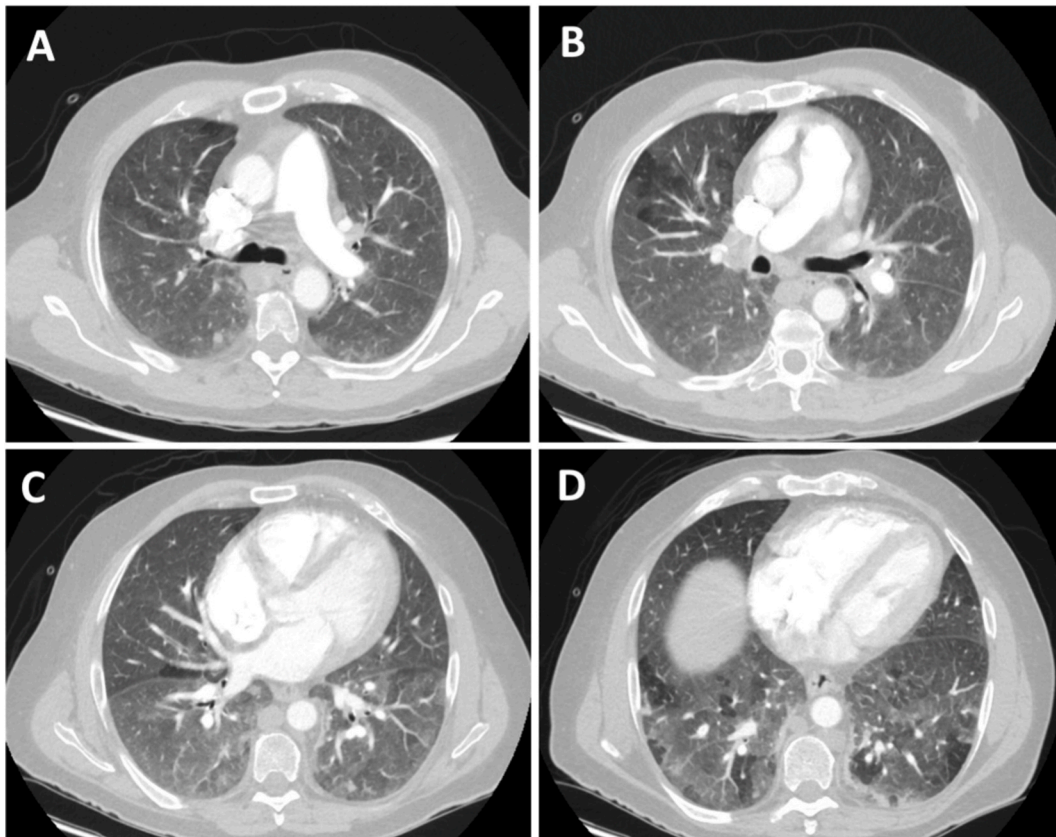


Fig. 1. High resolution CT of the chest performed without the administration of contrast was notable for micronodularity, ground glass opacities, and mosaic attenuation that was accentuated upon exhalation, suggestive of air trapping.

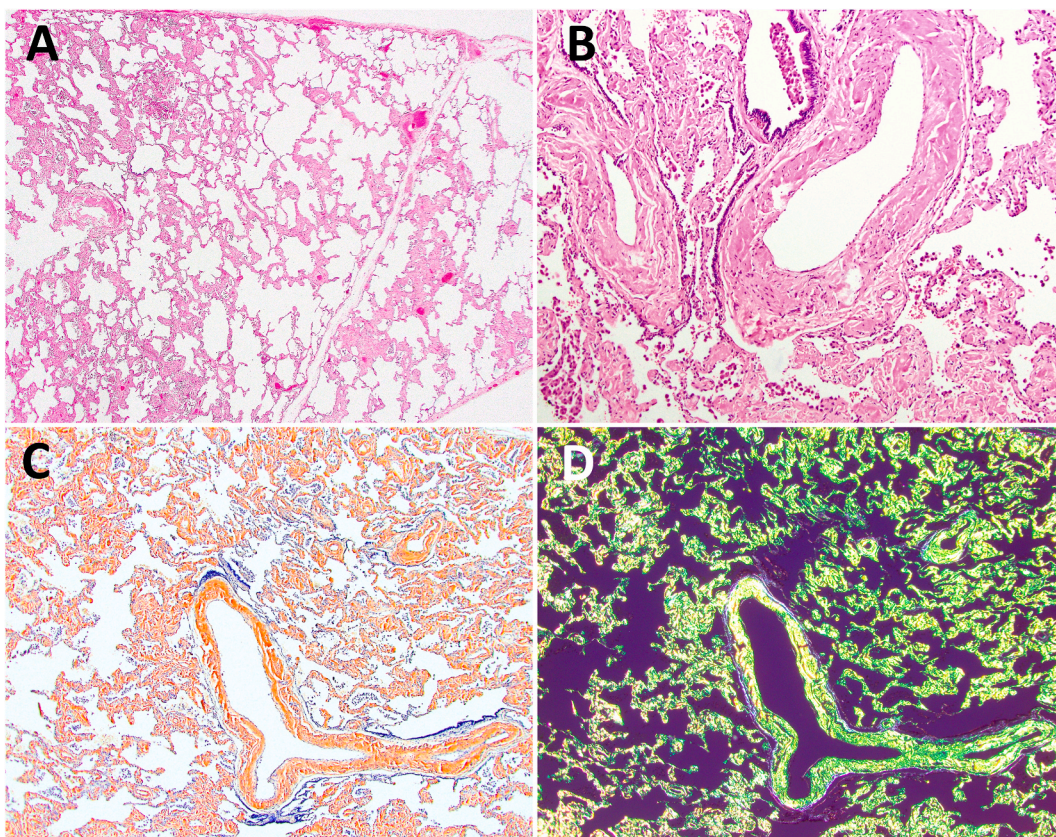


Fig. 2. Histopathologic findings on the diagnostic VATS lung wedge resections. A-Low power view of the lung wedge resection demonstrating a interstitial infiltration (H&E stain, 20× original magnification). B-Higher power view demonstrating the waxy, pink, amorphous deposition of amyloid in the walls of the vessels, the airways, and the parenchymal interstitium (H&E stain, 100× original magnification). C-Congo red stain highlighting the orangeophilic amyloid deposits viewed under non-polarized light, that (D) shows the characteristic apple-green birefringence when viewed under polarized light (40× original magnification).

hemosiderosis, as described in some case reports of pulmonary amyloidosis, are possible but less likely without clear radiologic or pathologic evidence of such [6].

In symptomatic patients, the diagnosis of pulmonary amyloidosis is further complicated by the wide array of potential clinical and radiologic manifestations, as well as the lack of a pathognomic presentation. Dyspnea and non-productive cough are usually the predominant symptoms, with hemoptysis, hoarseness, and pleuritic pain less common [5,7,8]. Diagnostic imaging, which should include high-resolution computed tomography (HRCT), reveals a variety of patterns depending on the histopathologic type ranging from solitary or multiple pulmonary nodules (nodular type) to diffuse findings including reticular opacities, septal thickening, and confluent consolidations with basal and peripheral predominance (diffuse alveolar-septal type) [9]. Again, these findings are nonspecific and can reflect many disease entities, confounding diagnostic accuracy [10]. In the case of our patient, radiologic findings were initially attributed to volume overload and further work-up was only pursued when aggressive ultrafiltration with dialysis did not lead to improvement. The diagnostic gold standard is still based on tissue diagnosis with histological evaluation including Congo red staining [2].

While a variety of histopathologic forms of pulmonary amyloidosis exist, diffuse forms of pulmonary involvement more commonly arise in the setting of systemic amyloidoses such as multiple myeloma [8,11]. In our patient, histopathologic evaluation of the lung revealed diffuse airway, parenchymal, and vascular amyloid deposition, which manifested as a restrictive ventilatory pattern with air trapping, gas exchange abnormality, and pre-capillary pulmonary arteriopathy, respectively. Although amyloid deposition in the airways, interstitium, and vasculature of the lung has been described, this rarely occurs in tandem. Ege and colleagues (2006) report a case of multiple myeloma and AL amyloidosis presenting with respiratory symptoms, restrictive disease, and diffuse interstitial infiltration on CT that ultimately demonstrated amyloid deposits in the bronchiolar walls on transbronchial biopsy without mention of interstitial or vascular involvement [7]. Conversely, other cases detail isolated pulmonary hypertension with amyloid deposits found only in the pulmonary vasculature on histopathology, although biopsy in these cases is not always performed and a presumptive diagnosis may be made based on the presence of systemic amyloidosis and pulmonary hypertension discovered on noninvasive imaging modalities or right heart catheterization [12–16]. To our knowledge, there is only one other reported case of proven tri-compartmental involvement of pulmonary amyloidosis in a patient presenting with dyspnea and ultimately found to have multiple myeloma [17]. However, this patient did not appear to undergo right heart catheterization and was not diagnosed with pulmonary

hypertension. These clinical narratives serve to emphasize the paucity of clear pathophysiologic and clinical associations in the literature due to incomplete invasive diagnostic testing or obscuring clinical history. While the pulmonary work-up was thorough in the case of our patient, we were not able to definitively confirm the presence or absence of amyloidosis affecting other organ systems.

4. Conclusion

We present a distinctive case of pulmonary amyloidosis in which amyloid deposits within all three compartments of the lung have resulted in clear clinical and physiologic consequences. As such, we provide a striking example of the spectrum of pulmonary abnormalities that can be produced by amyloid deposition, and the rapidity and severity with which this disease can affect pulmonary function.

Declaration of competing interest

RH reports receiving the following: indirect clinical trial research funding from Boehringer Ingelheim, Regeneron, and Galapagos; authorship fees from Dynamed and Wolters Kluwer; consulting fees from Teladoc, ImpactNetwork, Boehringer Ingelheim, and Paradigm Medical; advisory board meeting fees from Boehringer Ingelheim.

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All other authors report no conflicts of interest.

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