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CASE REPORT

ADVANCED

CLINICAL CASE: ACC.23

Hemoptysis After Heart Transplantation Caused by Pulmonary Amyloidosis

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ABSTRACT

Pulmonary involvement is a common sequela of systemic amyloidosis, occurring in up to 50% of cases. The patterns of involvement include focal nodular, diffuse interstitial, and tracheobronchial. This can lead to a variety of symptoms, including cough and shortness of breath. Although hemoptysis is not uncommon, massive hemoptysis is rare. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;13:101729) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 70-year-old man presented to the hospital with massive hemoptysis and a syncopal episode. Upon arrival to the emergency department, he was intubated for airway protection. His heart rate was 102 beats/min, and his blood pressure was 95/55 mm Hg. The physical examination was notable for blood in the endotracheal tube, regular heart rate and rhythm without murmurs, lungs clear to auscultation bilaterally, and extremities warm without edema. His laboratory values were remarkable for a white blood cell count of 11.6 × 1,000/μL and hemoglobin of 8.2 g/dL, with a creatinine of 2.1 mg/dL (baseline = 1.1 mg/dL) and lactate of 4.1 mmol/L.

LEARNING OBJECTIVES

- To recognize pulmonary amyloidosis as a possible diagnosis in an individual with known systemic amyloidosis.
- To understand the role of extracardiac manifestations of amyloidosis.

PAST MEDICAL HISTORY

The patient had a heart transplant 1 year before admission for nonischemic cardiomyopathy secondary to transthyretin cardiac amyloidosis from the V142I variant. His other medical problems included amyloid neuropathy and Stage 3 chronic kidney disease attributed to cardiorenal syndrome and calcineurin inhibitor toxicity. His medications included tacrolimus, mycophenolate mofetil, and patisiran.

It is of note that the patient was also hospitalized 6 months prior for mild hemoptysis. A right lower lobe masslike consolidation was noted on computed tomography angiography of the chest, and the patient underwent bronchoscopy with transbronchial biopsies. The pathology demonstrated scant alveolated lung parenchyma with focal amyloid deposits. He was initially treated with antibacterial and antifungal agents, which were ultimately discontinued when his cultures and serologies were essentially negative for infection. Surveillance imaging with close monitoring was planned. He underwent a positron emission tomography scan that demonstrated a decrease in the

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ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light chain

size of the right lower lobe mass. The lesion demonstrated moderate metabolic activity with a maximum standardized uptake value of 4.3. A 3-month follow-up film demonstrated no change in the right lower lobe mass, and he underwent a repeat bronchoscopy with repeat transbronchial biopsies. No malignancy was identified, and he was again noted to have interstitial amyloidosis. He was awaiting a follow-up visit with hematology but presented with massive hemoptysis.

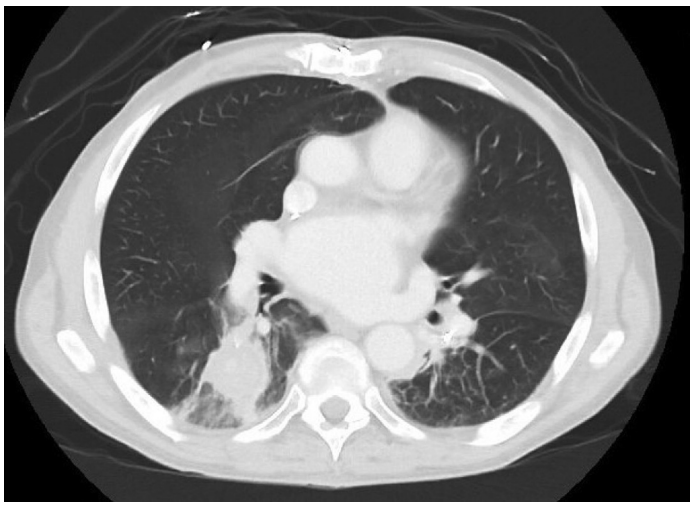
DIFFERENTIAL DIAGNOSIS

Given the patient's history of variant transthyretin amyloidosis and previous biopsy of a lung mass consistent with amyloidosis, pulmonary amyloid was high on the differential. However, massive hemoptysis is not a classical presentation of nodular amyloidosis. Other potential diagnoses included infections, especially of fungal etiology; arteriovenous malformation; malignancy; and diffuse alveolar hemorrhage.

INVESTIGATIONS

A chest computed tomography scan with contrast showed a 2.7-cm rounded contrast-filled structure in the posterior right lower lobe concerning for possible pulmonary arterial pseudoaneurysm (**Figure 1**). Bronchoscopy demonstrated oozing in the right lower lobe thought to be caused by a ruptured blood vessel. Esophagogastroduodenoscopy revealed a large amount of retained food and fluid in the stomach suggestive of gastroparesis without evidence of active bleeding. He underwent repeat bronchoscopy with biopsy of the lung mass that showed amyloid involvement.

FIGURE 1 Computed Tomography Scan With Contrast of Chest Showing Pulmonary Nodule



MANAGEMENT

Because of the persistent oozing from the endotracheal tube with concern for pseudoaneurysm as seen on the computed tomography scan, he underwent interventional radiology-guided embolization of a 25-mm superior segment right lower lobe pulmonary artery pseudoaneurysm with a 5-mm microvascular plug near the pulmonary mass (**Figure 2**). He subsequently underwent right lower lobe lobectomy to definitively remove the bleeding source. Biopsy showed diffuse interstitial and patchy perivascular amyloid deposition without evidence of underlying malignancy (**Figures 3 and 4**). Amyloid subtyping indicated transthyretin amyloid with the V142I variant.

DISCUSSION

Amyloidosis is a progressive disease that can present in various forms based on protein deposition. Transthyretin, previously known as prealbumin, is synthesized by the liver and abnormally deposited in tissue in transthyretin amyloidosis, whereas monoclonal immunoglobulin light chain (AL) is deposited in AL amyloidosis.[1] Transthyretin amyloidosis can either be inherited in an autosomal dominant pattern in variant transthyretin amyloidosis or present de novo in wild-type transthyretin amyloidosis. It classically deposits in the autonomic and peripheral nervous system and/or cardiovascular structures. Transthyretin amyloidosis cardiomyopathy has a prevalence of 5 per 100,000 and is more commonly noted in men (70%) with an average age at diagnosis of 73 years and a median survival from diagnosis of 37.6 months.[2]

Pulmonary manifestations of amyloidosis can include nodular parenchymal, diffuse alveolar-septal, and tracheobronchial involvement.[3] In an analysis of 223 autopsies of individuals with confirmed amyloidosis at Johns Hopkins Hospital over 80 years, pulmonary involvement was found in 68 (30%), with only 2 from cases of familial cardiomyopathy.[4] Interestingly, transthyretin amyloidosis involving the lung is exceedingly rare. In an analysis of 58 autopsy cases with known amyloidosis and pulmonary involvement at autopsy, 4 (7%) had transthyretin amyloidosis amyloid.[5]

The cause for our patient's hemoptysis was pulmonary amyloid based on biopsy results showing

interstitial amyloid deposition. Although lung involvement is a known manifestation of primary amyloidosis, it is rarely documented. The authors acknowledge that the patient's former biopsy 6 months before the event may have contributed to pseudoaneurysm formation and subsequent hemoptysis. However, it is believed that the extensive amyloid deposition seen on biopsy likely led to friability of the tissue that ultimately bled. Because the hemorrhage was so extensive, the pathologists were unable to determine the true nature of the pseudoaneurysm.

Unfortunately, despite the heart transplant, extracardiac manifestations may progress after. The patient was receiving patisiran, a transthyretin gene silencer, for amyloid neuropathy. Patisiran has not been studied in patients with pulmonary amyloid involvement, especially because transthyretin amyloidosis rarely presents in the lung.

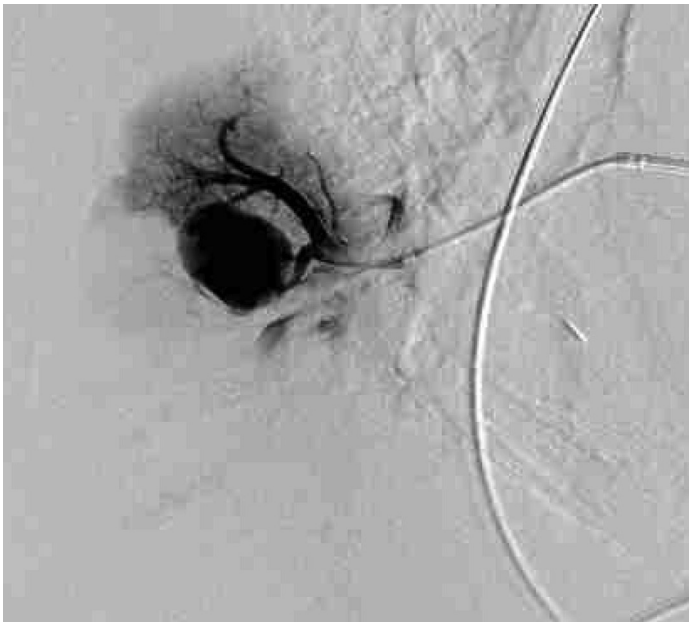
Diffuse alveolar-septal amyloidosis is classically associated with primary systemic amyloidosis. It presents as widespread deposition of small vessels and interstitium, with notable micronodules, interlobular septal thickening, and reticular opacities.[6] A computed tomography scan may show interlobular septal thickening in a basilar and peripheral distribution as well as confluent consolidations with additional foci of calcification. Although typically associated with AL amyloidosis, pulmonary involvement in transthyretin amyloidosis amyloid has been documented.[7]

The gold standard for diagnosis is histopathologic with biopsy showing evidence of apple-green birefringence using Congo red staining.[8] False positives may occur because of improper staining techniques, and false negatives can result from an inadequate sample size. Further immunohistologic analysis can assist with fibril type, and mass spectrometry is necessary for subtyping of AL vs transthyretin amyloidosis involvement.

In transthyretin amyloidosis amyloid, the p.V142I variant is the most common cause of variant or hereditary amyloidosis in the United States, present in 3% of African Americans. Hereditary amyloid typically presents with cardiomyopathy, peripheral and autonomic neuropathy, or as a combination of the 2. The median survival after diagnosis with the Val122Ile gene is about 2.5 years after diagnosis as opposed to 3.5 years in wild type.[9]

Despite no randomized trials assessing treatment specifically for pulmonary amyloid, it is thought that systemic treatment controlling the underlying process may help with further spread of the abnormal protein.[10] However, with significant parenchymal involvement, surgical resection or laser therapy may be considered.

FIGURE 2 Interventional Radiology-Guided Fluoroscopy of Pulmonary Pseudoaneurysm



FOLLOW-UP

He was seen in the cardiology and pulmonary clinic a couple weeks later without further hemoptysis and was reportedly able to exercise with no complaints of

FIGURE 3 Focal Amyloidosis Seen on Biopsy of Lung Nodule

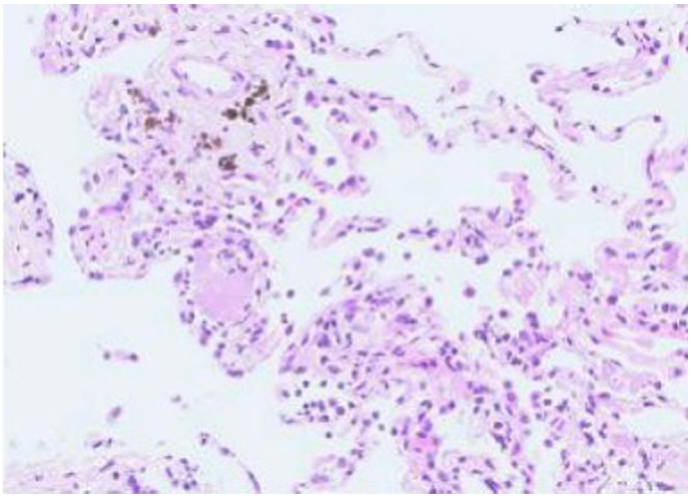
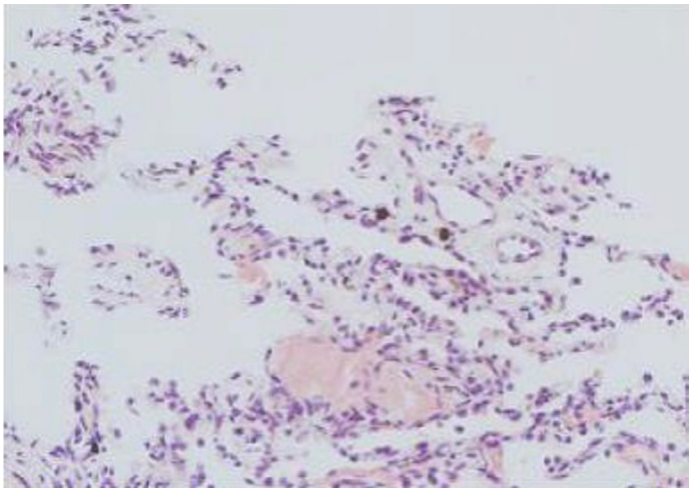


FIGURE 4 Congo Red Stain With Evidence of Amyloidosis on Lung Nodule



dyspnea. However, a few months later, he had reported a progressive cough. Chest computed tomography was repeated and showed multiple nodular densities bilaterally. Bronchoscopy was performed with bronchoalveolar lavage and biopsies of a nodule with an infiltrative lesion showing further hemorrhage and amyloid deposition.

CONCLUSIONS

We present a case of significant hemoptysis with biopsy-proven interstitial amyloidosis of the lung. When a patient with known amyloid presents with significant pulmonary symptoms, including progressive cough, dyspnea, or hemoptysis, pulmonary amyloid should be on the differential. There is no evidence that disease-directed therapy such as patisiran will impact the progression of pulmonary amyloidosis, and definitive treatment including resection of localized lesions may be required.

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