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Pulmonary amyloidosis presenting as lung cavitation with bronchiectasis: A case report

The case of a 60-year-old female whose initial clinical findings were ambiguous demonstrates the utility of amyloid subtype analysis.

ABSTRACT: Amyloidosis is the extracellular deposition of amyloid fibril protein in any tissue or organ. Pulmonary amyloidosis is a localized form of amyloid deposition that is confined to the lung parenchyma and can cause airway obstruction, dysphagia, and chronic pleural effusions. When a 60-year-old female presented with chronic cough and recalcitrant pneumonias she was sent for imaging investigations and found to have cavitation with bronchiectasis of the right upper lobe. The patient subsequently underwent diagnostic bronchoscopy and bronchoalveolar lavage to obtain specimens for testing. Cytological evaluation revealed pulmonary amyloidosis in the area of cavitation, and the patient was diagnosed with a monoclonal gammopathy of unknown significance. Given her autoimmune hepatitis and her monclonal gammopathy, her amyloid sample was subtyped using laser capture microdissection, liquid chromatography, and tandem mass spectrometry, and the patient was found to have AL kappa type amyloidosis stemming from her monoclonal gammopathy. Given the localized extent of her amyloidosis, chemotherapy was deferred and close clinical follow-up was planned. This case of pulmonary amyloidosis demonstrates the utility of amyloid subtype analysis in clinically ambiguous situations to determine further workup and future follow-up.

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Amyloidosis is the extracellular deposition of insoluble amyloid fibrilprotein in any tissue or organ.[1] The most common subtypes of the disease are AL amyloidosis and AA reactive amyloidosis.[1] AL amyloidosis is a systemic disease caused by immunoglobulin light chain fragments, while AA amyloidosis is a potential complication of recurrent inflammation leading to the production of serum amyloid A, an acute phase reactant.[2] Pulmonary amyloidosis is a localized form of amyloid deposition that is confined to the lung parenchyma.[3] Consequences of pulmonary amyloidosis include hoarseness, stridor, airway obstruction, dysphagia, chronic pleural effusions, and pulmonary hypertension.[4]

Case data

A 60-year-old female with a 6-month history of chronic cough and recalcitrant pneumonias was referred to a community respirologist. An X-ray image **[Figure 1]** and CT images **[Figure 2]** showed a cystic consolidation in the right upper lobe that was concerning for cavitation with bronchiectasis.

The patient's past medical history was notable for type 2 diabetes mellitus and autoimmune hepatitis with esophageal varices. The

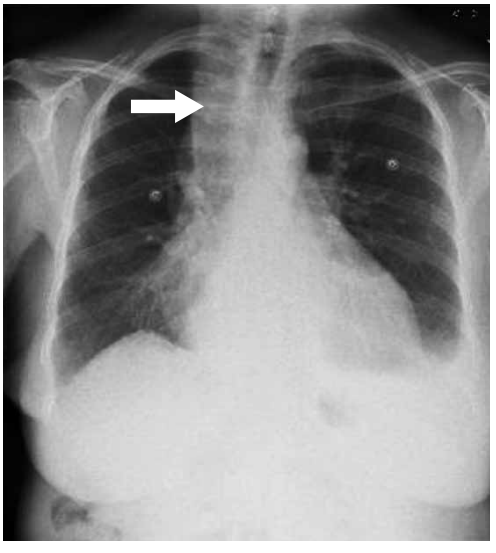


FIGURE 1. An anteroposterior radiograph shows right upper lobe consolidation (arrow).

initial differential diagnosis included infectious disease leading to cavitation and bronchiectasis, such as a polymicrobial bacterial infection, nocardiosis, actinomycosis, and tuberculosis. Malignancy and inflammatory conditions were also considered.

A bronchoscopy revealed a difficult-to-access right upper lobe with a friable endobronchial lining. Bronchoalveolar lavage was undertaken to obtain specimens for cytological evaluation, white blood cell count and differential, and bacterial, fungal, and mycobacterium cultures. Pulmonary amyloidosis was confirmed by cytology, with results from Congo Red staining considered diagnostic **[Figure 3]**.

As part of the workup for her newly diagnosed pulmonary amyloidosis, the patient underwent a serum protein electrophoresis test. A diagnosis of monoclonal gammopathy of unknown significance (MGUS) was made based on the presence of immunoglobulin class IgG and lambda type free light chain.[5] A urine protein electrophoresis test found no abnormalities. A bone marrow biopsy showed no advanced blood cell dyscrasias or amyloid deposition. No systemic signs of multiple myeloma were found, with tests revealing a normal serum calcium level, normal renal function, and no proteinuria. A skeletal survey revealed no lytic bone lesions. No cutaneous findings, heart failure findings, or peripheral neuropathies were identified when other organs likely to be affected by amyloidosis were assessed.[6]

Because of the multiple potential causes for the patient's pulmonary amyloidosis, including her previously known autoimmune hepatitis and newly diagnosed MGUS, the amyloid samples from her bronchoalveolar lavage were sent to the Mayo Clinic for further analysis. Testing revealed AL kappa type amyloid deposits. These findings pointed to the patient's amyloid lung deposition being secondary to

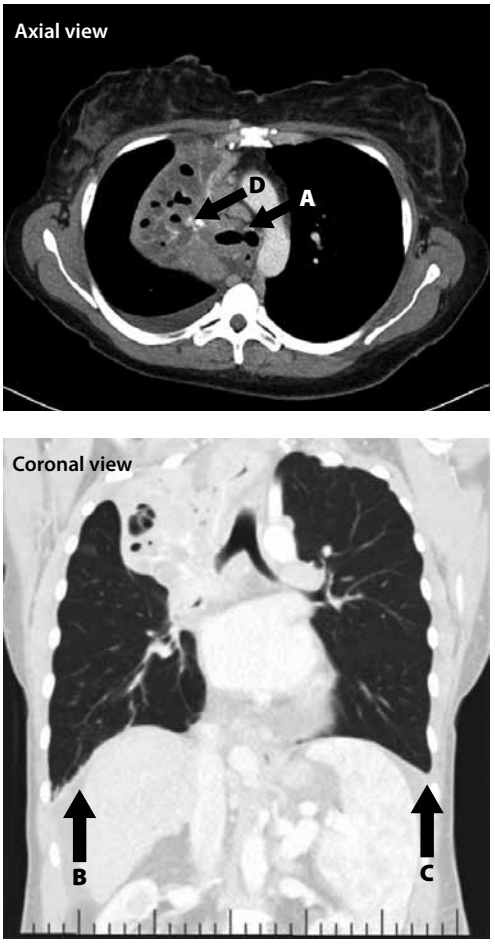


FIGURE 2. CT images show mass-like area of consolidation involving the entire right upper lobe. Central lucencies indicate multiple locules consistent with cavitation. Both coronal and axial views show that the right upper lobe bronchus is completely obstructed. Right-sided paratracheal lymph nodes (arrow A) can be seen. A small right-sided pleural effusion (arrow B), a minimal left-sided pleural effusion (arrow C), and calcification (arrow D) can also be seen.

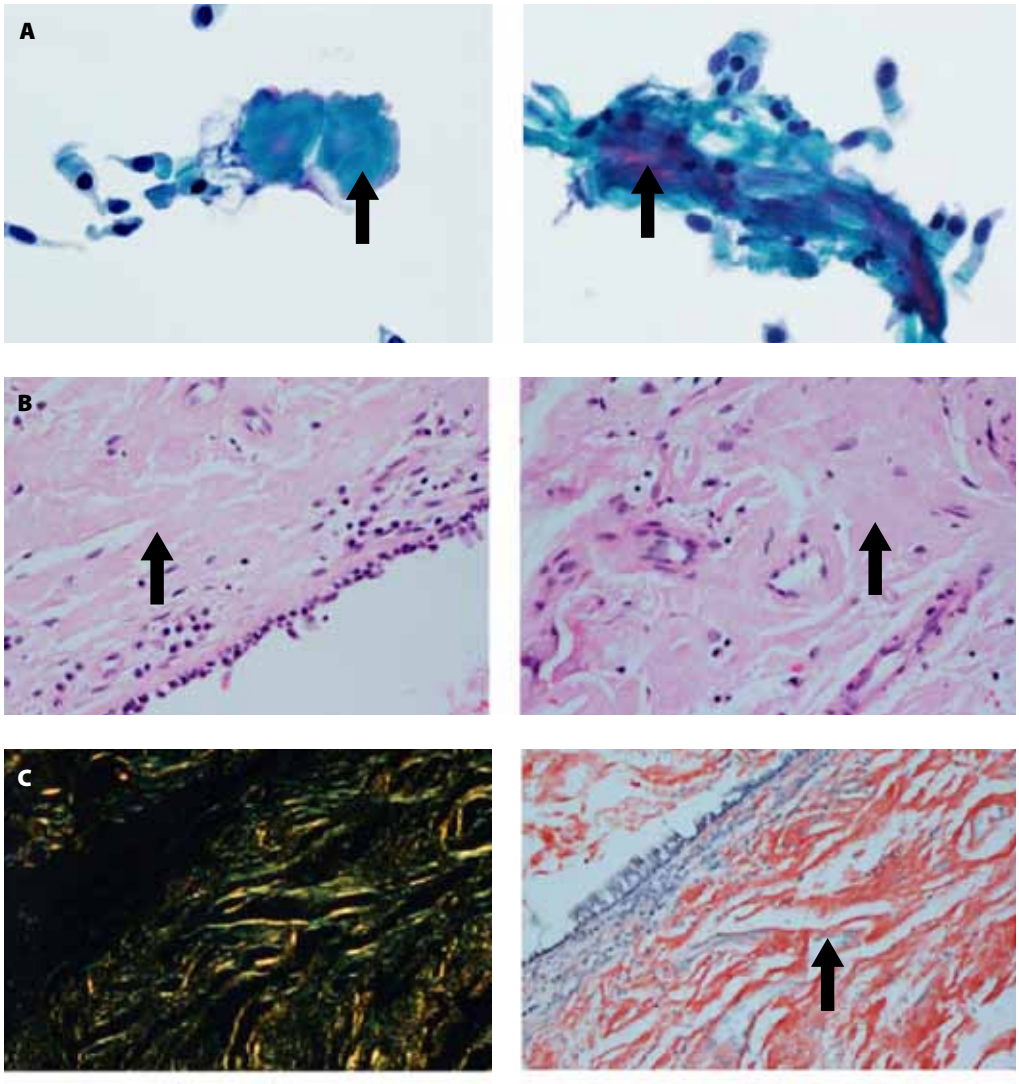


FIGURE 3. Cytological evaluation of fluid from bronchoalveolar lavage confirms pulmonary amyloidosis. A: Ciliated bronchial epithelial cells surrounded by dense cyanophillic material morphologically consistent with amyloid deposition (arrows). B: Tissue fragments of intact bronchial epithelium with salmon-pink amorphous deposition within the underlying interstitium and surrounding blood vessels (arrows). C: Apple-green birefringence under polarized light after Congo Red staining (arrow).

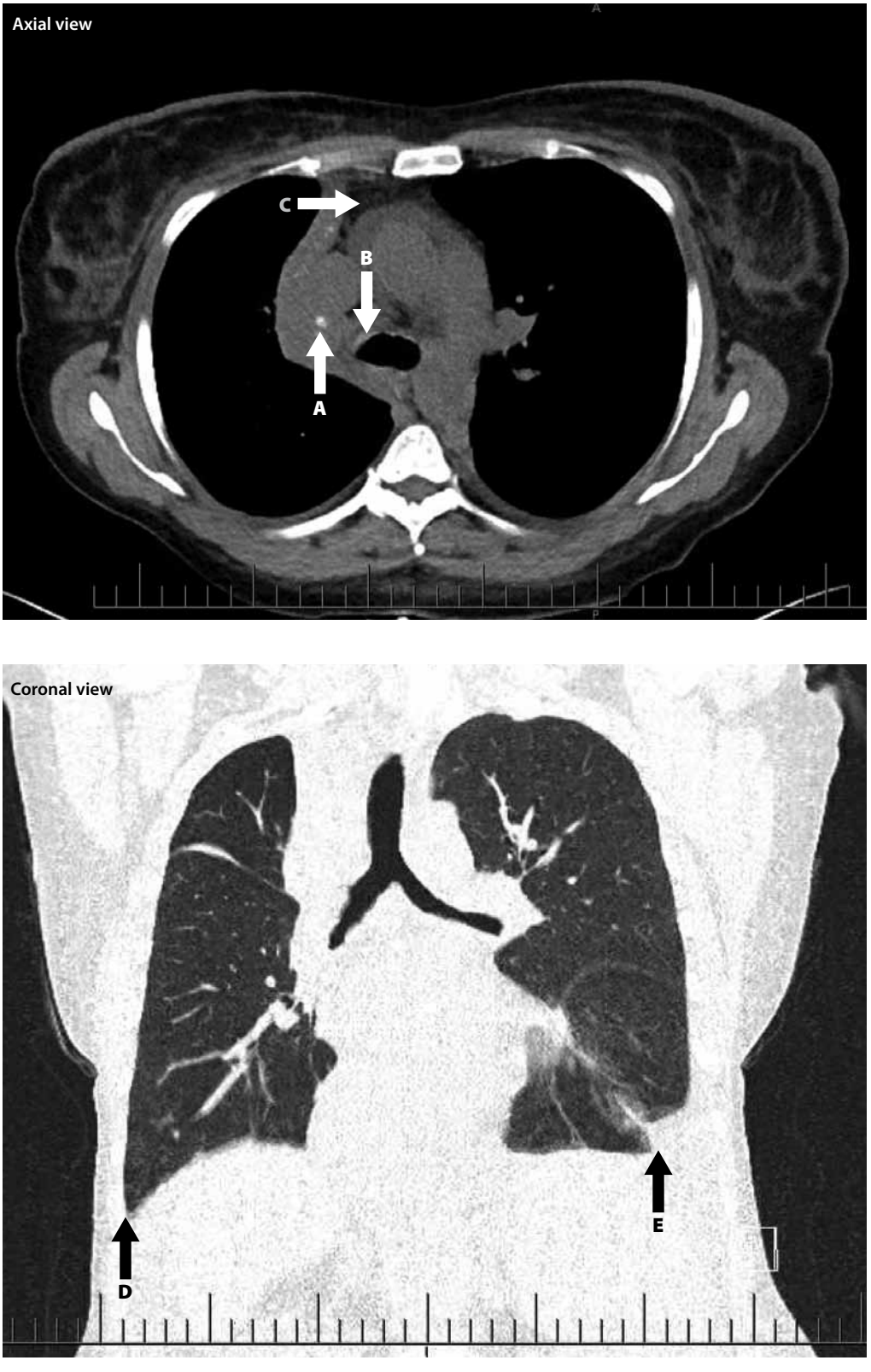


FIGURE 4. CT images obtained for reassessment of the patient reveal further collapse and consolidation of the right upper lobe and obstruction of the upper lobe bronchus. Regions of calcification (arrow A) can be seen within the area of collapse and consolidation, which may lie within the bronchus. Persistent enlargement of paratracheal lymph nodes (arrow B) can be seen. Since the initial CT images were obtained a pericardial effusion (arrow C) has become evident, the right-sided pleural effusion (arrow D) has decreased, and the left-sided pleural effusion has increased (arrow E).

her MGUS. Given the localized extent of the patient's amyloidosis, a decision was made in conjunction with the patient's hematologist to defer chemotherapy and plan for close clinical follow-up.

The patient was reassessed 5 months after her initial bronchoscopy. Although CT images obtained for reassessment showed a complete collapse of the right upper lobe **[Figure 4]**, her cough had resolved and her exercise tolerance remained normal. She had no classic signs of systemic amyloidosis on reassessment but was found to have atrial fibrillation, and her echocardiogram showed evidence of elevated pulmonary artery pressures, with a moderately elevated right ventricular systolic pressure of 53 mm Hg.

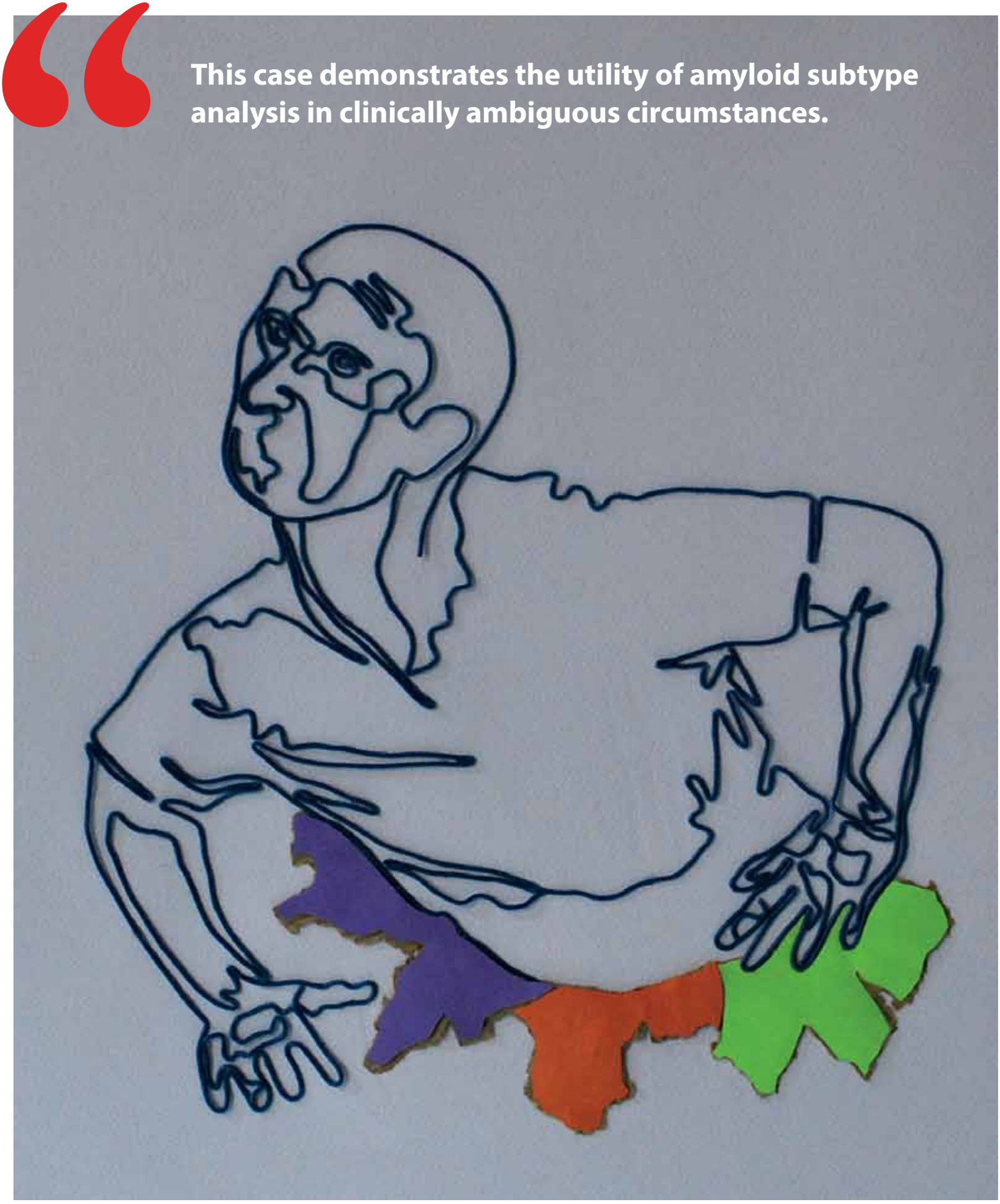
Discussion

In this case amyloid typing was necessary because there were at least two potential mechanisms for the patient's amyloidosis: her MGUS (AL amyloidosis) and her autoimmune hepatitis (AA amyloidosis). The diagnosis of AL amyloidosis could not be assumed based on the presence of monoclonal light chains in the serum because it is not uncommon for a patient with another form of amyloidosis to have a concomitant and unrelated MGUS.[5]

Historically, amyloid typing has been performed using immunohistochemistry and immunofluorescence analysis.[6] However, immunohistochemistry can yield inconclusive results because the antigenic epitope may be lost during tissue preparation and samples may be contaminated by serum proteins that result in high background staining.[7] The Mayo Clinic uses laser capture microdissection of clinical biopsy samples followed by liquefied chromatography combined with tandem mass spectrometry to identify the subtype of amyloid with a high degree of accuracy. Testing for this case revealed AL kappa type amyloid deposits and indicated the patient's amyloid lung deposition was secondary to her MGUS.

The elevated pulmonary artery pressures and atrial fibrillation found when the patient was reassessed are in keeping with reports that have cited pulmonary hypertension and lobar atelectasis as sequelae of AL pulmonary amyloidosis.[8-10] Increased left ventricular wall

This case demonstrates the utility of amyloid subtype analysis in clinically ambiguous circumstances.



thickness is the most common feature of cardiac amyloidosis[11] and was not seen in this patient, while atrial fibrillation, which affects up to 20% of systemic amyloidosis cases,[11] was eventually diagnosed in this patient.

Current management of amyloidosis is based on treatment of the underlying cause of the abnormal deposition of proteins in extracellular sites. Treatment may involve chemotherapy, immunosuppression, stabilizer proteins, or small interfering ribonucleic acids, depending on the amyloid subtype identified.[12] AL amyloidosis, which is caused by abnormal immunoglobulin light chain production by a plasma cell neoplasm, can be treated with high-dose chemotherapy and/or stem cell transplantation.[13,14] The preferred therapy for AA amyloidosis is control of the underlying inflammatory disease and thus suppression of serum amyloid protein production. ATTR amyloidosis, which is caused by a mutation in the transthyretin (TTR) gene, can be treated with liver transplantation or tafamidis, a chaperone protein for the stable form of transthyretin.[15]

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Given the risks associated with amyloidosis and the progressive nature of the disorder, a prognosis relies on accurate identification of specific amyloid subtypes, which can vary in invasiveness and require drastically different therapies. As the number of unique protein aggregates identified via tandem mass spectrometry increases and targeted therapies become more widely available, subtype identification will undoubtedly become more important.

Summary

The patient in this case was found to have cavitation with bronchiectasis in the right upper lobe, initially thought to be secondary to infection. She underwent a bronchoscopy and bronchoalveolar lavage. Based on cytological evaluation, including Congo Red staining, she was eventually diagnosed with pulmonary amyloidosis. Because of the multiple potential causes for this disorder, the patient's amyloid samples were sent to the Mayo Clinic for further analysis using laser capture microdissection, liquid chromatography, and tandem mass spectrometry. Testing revealed AL kappa type amyloid deposits and contributed to the decision made to defer chemotherapy and plan for close clinical follow-up.

This case demonstrates the utility of amyloid subtype analysis in clinically ambiguous circumstances. Management of localized pulmonary amyloidosis is dependent on the severity of symptoms, and asymptomatic patients may not require treatment. ■

Competing interests

None declared.

References

1. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid 2010;17:101-104.
2. Kyle RA. Amyloidosis: A convoluted story. J Haematol 2001;114:529-538.
3. Suzuki H, Matsui K, Hirashima T, et al. Three cases of the nodular pulmonary amyloidosis with a long-term observation. Intern Med 2006;45:283-286.
4. Dahl KA, Kernstine KH, Vannatta TL, et al. Tracheobronchial amyloidosis: A surgical disease with long-term consequences. J Thorac Cardiovasc Surg 2004;128:789-792.
5. Guidelines Working Group of UK Myeloma Forum; British Committee for Standards in Haematology, British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol 2004;125:681-700.
6. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 2005;79:319-328.
7. Holub D, Flodrova P, Pika T, et al. Mass spectrometry amyloid typing is reproducible across multiple organ sites. BioMed Res Int 2019. doi: 10.1155/2019/3689091.
8. Cirulis MM, Emerson LL, Bull DA, et al. Pulmonary arterial hypertension in primary amyloidosis. Pulm Circ 2016;6:244-248.
9. Eder L, Zisman D, Wolf R, Bitterman H. Pulmonary hypertension and amyloidosis—an uncommon association: A case report and review of the literature. J Gen Intern Med 2007;22:416-419.
10. Price LC, McAuley DF, Marino PS, et al. Pathophysiology of pulmonary hypertension in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2012;302:L803-L815.
11. Murtagh B, Hammill SC, Gertz MA, et al. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol 2005;95:535.
12. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med 2013;369:819-829.
13. Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: A retrospective review from a tertiary referral center. Bone Marrow Transplant 2013;48:1302-1307.
14. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015;126:612-615.
15. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: A randomized, controlled trial. Neurology 2012;79:785-792.