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CASE REPORT

ADVANCED

CLINICAL CASE

Constrictive Pericarditis Revealing Rare Case of ALH Amyloidosis With Underlying Lymphoplasmacytic Lymphoma (Waldenstrom Macroglobulinemia)

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ABSTRACT

We present a case of pericardial amyloidosis with associated lymphoplasmacytic lymphoma in a patient with chronic worsening shortness of breath and cough. This case highlights the wide variation in the presentation of cardiac amyloidosis, and the rare occurrence of clinically significant light-chain and heavy-chain amyloidosis in the pericardium. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:271–275) © 2022 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

An 80-year-old woman with a recent admission for pleural effusions presented to our hospital for insidiously worsening shortness of breath and cough. When she initially presented to an outside hospital, she was found to have pleural effusions and underwent a thoracentesis, the result of which was negative for malignancy.

Upon presentation, her blood pressure was 127/91 mm Hg, her heart rate was 95 beats/min, and her respiratory rate was 27 breaths/min. Examination revealed bilateral dullness to percussion and diminished breath sounds with scattered crackles throughout lung fields. Cardiac examination revealed a systolic ejection murmur, which was loudest at the right upper sternal border, and no lower extremity edema.

LEARNING OBJECTIVES

- To be able to make a differential diagnosis of causes of constrictive pericarditis.
- To appropriately diagnose atypical presentations of ALH amyloidosis using laboratory studies and multimodal imaging techniques.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AH = heavy chain form of amyloidosis

AL = light chain form of amyloidosis

ALH = light-chain and heavy-chain amyloidosis

CMR = cardiac magnetic resonance imaging

ECG = electrocardiogram

TTE = transthoracic echocardiography

MEDICAL HISTORY

The patient had a history of hypertension, hyperlipidemia, gastritis, and uterine fibroids.

DIFFERENTIAL DIAGNOSIS

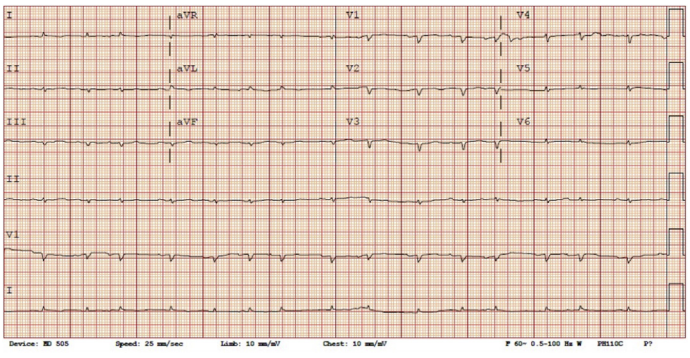
The differential diagnosis of causes of constrictive pericarditis includes prior radiation therapy; prior cardiac surgery; *Mycobacterium tuberculosis* infiltration or other bacterial, viral, or fungal causes; autoimmune causes such as rheumatoid arthritis or systemic lupus erythematosus; and neoplastic causes including carcinoma of the breast, lung, or colon; amyloidosis; lymphoma; leukemia; sarcoma; or mesothelioma.

INVESTIGATIONS

Electrocardiogram (ECG) on admission revealed low voltages (Figure 1), initially attributed to the pericardial effusion. However, after creation of a pericardial window to treat concern for tamponade from the pericardial effusion, low voltages on ECG continued to persist (Figure 2). Troponin I was normal, and N-terminal pro-B-type natriuretic peptide was 3,641 pg/mL. Transthoracic echocardiography (TTE) showed a left ventricular ejection fraction of 69% and a large pericardial effusion.

Autoimmune, infectious, and neoplastic investigations were pursued. Laboratory studies revealed a decreased complement component 3 of 74 mg/dL and complement component 4 of 11 mg/dL.

FIGURE 1 Initial Electrocardiogram



Diffuse low voltages on electrocardiogram, initially attributed to pericardial effusion.

Serum protein electrophoresis with immunofixation revealed IgM λ M protein of 1.1 g/dL. Serum free κ light chains were normal at 1.1 mg/dL, serum free λ light chains were mildly elevated at 3.7 mg/dL, and the κ-to-λ free light chain ratio was low normal at 0.3. The results of all laboratory studies evaluating for infectious causes were negative. Positron emission tomography imaging was unrevealing, with no cardiac or lymph node uptake.

Serial TTEs revealed a small left ventricle with normal function, normal right ventricle size with mildly reduced right ventricular systolic function, and progressive pericardial thickening with a septal bounce typical of constrictive physiology (Figures 3 and 4). Although the medial and lateral mitral annular e' velocities were <8 cm/s, the medial velocity was greater than the lateral, the mitral inflow E/A ratio was 1.6, and there was an exaggerated end-diastolic expiratory hepatic flow reversal suggestive of constrictive physiology. This consideration was further reinforced by respiratory variation in the left ventricular outflow tract and mitral inflow velocities. By contrast, restrictive cardiomyopathies classically demonstrate e' velocities <8 cm/s and E/e' >15, without septal bounce, respiratory variation in the left ventricular outflow tract and mitral inflow velocities, or end-diastolic expiratory hepatic vein flow reversal. Furthermore, there was no evidence of aortic stenosis on TTE to explain the incidental finding of the systolic ejection murmur found on physical examination.

Cardiac magnetic resonance (CMR) showed biatrial enlargement, diffuse mild pericardial thickening measuring ≤4 mm, and diffuse postcontrast late gadolinium hyperenhancement and diastolic septal bounce during inspiration consistent with constrictive pericarditis (Figure 5) of an inflammatory type. There was no myocardial T2 hyperintensity or focal late gadolinium enhancement to suggest myocarditis. There was normal nulling of the myocardium on postcontrast Look Locker TI scout images and no abnormal late gadolinium enhancement to suggest myocardial amyloid infiltration.

The patient underwent thoracentesis, video-assisted thoracoscopic surgery for decortication and talc pleurodesis, and pericardial window. Microscopic evaluation of the pericardium revealed large nodular aggregates of amorphous extracellular protein. A Congo red stain highlighted the amorphous material, which supported the presence of amyloid protein (Figures 6 and 7). Further confirmatory studies as well as subtyping by liquid chromatography tandem mass spectrometry revealed λ light chain and μ heavy chain

ALH-type amyloid deposition. Notably, patchy lymphoplasmacytic inflammation was also noted in association with the amyloid protein. Immunohistochemical stains demonstrated this population to be positive for IgM. Subsequent polymerase chain reaction to evaluate for an MYD88 mutation revealed an MYD88 L265P alteration. Together with the recent results of serum protein electrophoresis with immunofixation showing IgM λ M protein at 1.1 g/dL and a λ light chain–predominant B-cell population identified by peripheral blood flow cytometry, the findings were consistent with lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia) with associated ALH amyloidosis.

MANAGEMENT

After thoracoscopic surgery and pericardial window, the patient had persistent hypotension postoperatively and new-onset atrial fibrillation, thus was admitted to the intensive care unit for stabilization. Given the patient's fragility and comorbidities, she was deemed not to be a candidate for pericardial stripping and was treated conservatively with diuresis. After discussion with amyloid specialists, it was determined that the patient was not a candidate for chemotherapy or immunotherapy, given her poor functional status with refractory heart failure and hypotension.

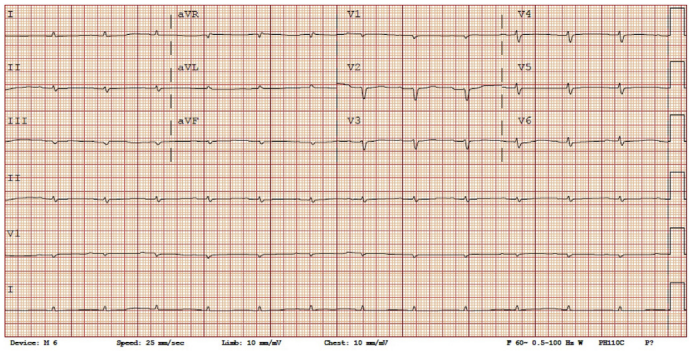
DISCUSSION

Cardiac amyloidosis presenting as constrictive pericarditis is exceptionally rare, given that the typical manifestations of cardiac amyloidosis involve direct involvement of the myocardium. Involvement of the pericardium and manifestations of cardiac tamponade have been described in only a few single case reports.[1-3] Any clonal process resulting in clonal light chain or heavy chain production, including lymphoplasmacytic lymphoma in our case, can be associated with the light chain form or the heavy chain form of amyloidosis, although most cases are associated with plasma cell dyscrasias.

One of the most important diagnostic clues for constrictive pericarditis is low voltage on ECG. Echocardiography can show ventricular septal motion abnormality, mitral annulus e' ≥8 cm/s, respiratory variations with mitral and tricuspid inflow values, or end-diastolic expiratory hepatic vein flow reversal. CMR techniques can also aid in the evaluation of pericardial thickening, enhancement, and assessment of hemodynamic changes, including constrictive physiology.[4] Pericardial biopsy has been the standard for definitive diagnosis of amyloidosis of the pericardium.

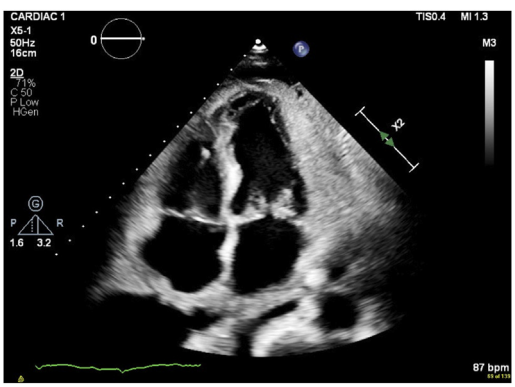
Given the patient's N-terminal pro-B-type natriuretic peptide of >1,800 pg/mL and tumor burden estimated by difference between involved and uninvolved free light chains of 2.6 mg/dL, the patient would be categorized as having stage II AL amyloidosis under the Mayo 2012 staging system, which is associated with a median overall survival of 72 months.[5] However, prior staging and prognosis have primarily been from patients with infiltrative myocardial amyloid, and the true prognosis of amyloidosis manifesting as constrictive pericarditis is unknown.

FIGURE 2 Subsequent Electrocardiogram After Pericardial Window



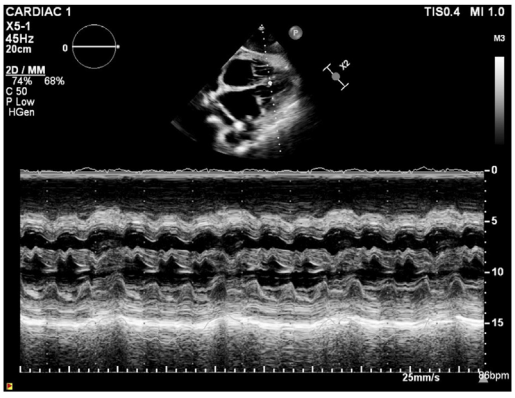
Persistent low voltages after creation of a pericardial window.

FIGURE 3 Transthoracic Echocardiogram Demonstrating Constriction



Apical 4-chamber view with pericardial thickening.

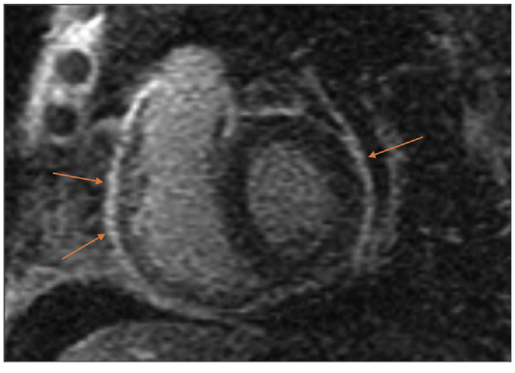
FIGURE 4 Transthoracic Echocardiogram Demonstrating Septal Bounce



Subcostal M-mode demonstrating abnormal septal motion.

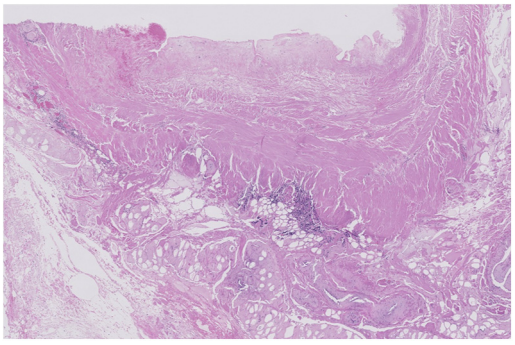
The optimal treatment for lymphoproliferative neoplasms associated with amyloidosis is chemotherapy or immunotherapy directed at the clonal cells.[6] However, such treatment generally aims to prevent further amyloid fibril deposition, rather than lead to substantial regression of deposits. In this patient's case, she had end-stage heart failure related to constrictive pericarditis at the time of diagnosis, without any good therapeutic options. If patients can tolerate procedures, surgical options for therapy could include pericardiectomy to remove the hemodynamic effects of existing amyloid accumulation.

FIGURE 5 Cardiac Magnetic Resonance With Pericardial Enhancement



Diffuse pericardial thickening measuring ≤4 mm and diffuse postcontrast late gadolinium hyperenhancement demonstrating constrictive pericarditis.

FIGURE 6 Surgical Pathologic Analysis of Pericardium



Pericardium and pericardial soft tissue with patchy aggregates of amorphous extracellular amyloid protein and focal lymphoplasmacytic inflammation.

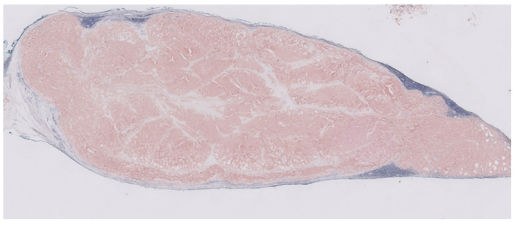
FOLLOW-UP

The patient continued to have refractory heart failure with hypotension. She declined further invasive procedures and treatment options and opted to spend time at home with her family.

CONCLUSIONS

We diagnosed a rare case of pericardial involvement of amyloid deposits associated with lymphoplasmacytic lymphoma. The constrictive physiology was driven by amyloid deposition associated with pericardial inflammation from the lymphoplasmacytic lymphoma. CMR and biomarkers did not show true myocardial amyloid deposition; rather, the deposition occurred on serosal surfaces of the pericardium. Although rare, pericardial amyloidosis should be considered in those with constrictive physiology.

FIGURE 7 Pericardium With Amyloid Deposition



A Congo Red stain demonstrating deep red staining of extracellular protein.

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Dr Witteles has served on advisory boards for Pfizer, Alnylam, Ionis, Regeneron, Eidos, and Janssen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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