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CASE REPORT

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Coexistence of Light Chain and Transthyretin Cardiac Amyloidosis

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ABSTRACT

Although most patients with cardiac amyloidosis are diagnosed with either light chain (AL) or transthyretin (ATTR) disease, coexisting amyloid subtypes can occur. We present three cases of coexisting AL and ATTR cardiac amyloidosis and demonstrate the importance of clinical history and endomyocardial biopsy in diagnosis of this rare entity.
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Cardiac amyloidosis is characterized by deposition of insoluble amyloid fibrils in the myocardium leading to heart failure (HF), with light chain amyloid cardiomyopathy (AL-CM) and transthyretin amyloid cardiomyopathy (ATTR-CM) accounting for 95% of cases.[1] Current diagnostic algorithms center on pursuit of tissue biopsy to identify AL-CM in the presence of an abnormal monoclonal protein screen; however, it is important to recognize that biopsy may instead demonstrate ATTR-CM. Additionally, there are few reports of coexisting AL and ATTR-CM.[2,3] At our center, 207 patients with ATTR-CM underwent endomyocardial biopsy, of whom 83 (40%) had abnormal free light chain test results between 2002 and 2023. Here, we present the 3 cases of concomitant AL and ATTR-CM and illustrate how integration of patient demographics and clinical history is necessary for prompt diagnosis of this rare entity.

LEARNING OBJECTIVES

- To understand the presenting signs and symptoms of cardiac amyloidosis, including noncardiac features associated with the disease.
- To recognize clinical features associated with coexisting light chain and transthyretin cardiac amyloidosis.
- To understand the indications for endomyocardial biopsy in the diagnosis of cardiac amyloidosis.

PATIENT 1

An 83-year-old African-American man with a history of hypertension, severe aortic stenosis treated with transcatheter aortic valve replacement, lumbar spinal

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ABBREVIATIONS AND ACRONYMS

AL-CM = light chain amyloid cardiomyopathy

ATTR-CM = transthyretin amyloid cardiomyopathy

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LVH = left ventricular hypertrophy

MM = multiple myeloma

NT-pro-BNP = N-terminal pro-B type natriuretic peptide

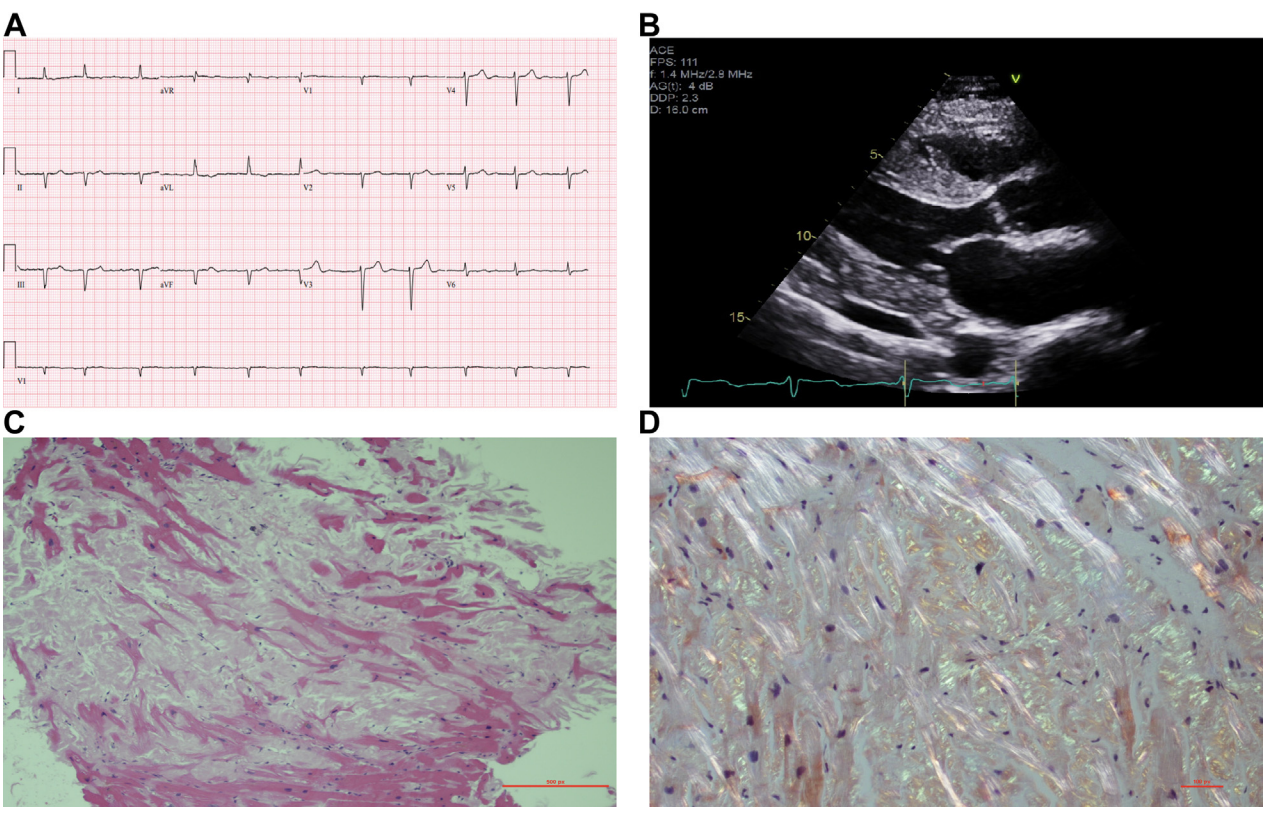
stenosis, and bilateral carpal tunnel syndrome presented with 1 month of dyspnea on exertion. On examination, he had jugular venous distension and peripheral edema. Electrocardiogram showed low voltage and atrial fibrillation with slow ventricular response (Figure 1). Echocardiogram demonstrated concentric left ventricular hypertrophy (LVH), ejection fraction (EF) of 60% to 65%, and biatrial enlargement. Serum light chain test results were abnormal (κ/λ ratio of 113), and results of examination of bone marrow biopsy specimen were consistent with multiple myeloma (MM).

His presentation with HF with preserved ejection fraction (HFpEF) was presumed to be secondary to AL-CM overlapping with MM, and he was initiated on lenalidomide, daratumumab, and dexamethasone (DaraRd) for treatment. Although a tissue biopsy was not needed to further guide AL-CM/MM treatment, endomyocardial biopsy was pursued because of a suspicion for concurrent ATTR-CM. given the presence of specific comorbidities, including severe aortic stenosis, bilateral carpal tunnel syndrome, and lumbar spinal stenosis. The biopsy specimen demonstrated AL (κ) and wtATTR deposition identified by mass spectrometry. He was initiated on tafamidis and continues to do well 1 year after diagnosis (Table 1).

PATIENT 2

A 90-year-old Caucasian man with a history of atrial fibrillation and hypertension presented with weakness and hypoxic respiratory failure. On physical examination, he had jugular venous distention. Laboratory data were significant for an NT-proBNP of 5,798 pg/mL. Echocardiogram showed an EF of 70% to 75%, moderate LVH, severe biatrial enlargement, and moderate aortic stenosis. Serum light chains were abnormal (κ/λ ratio of 31.39).

FIGURE 1 Electrocardiogram, Echocardiogram, and Endomyocardial Biopsy Images From a Patient Diagnosed With Co-Existing Light Chain and Transthyretin Cardiac Amyloidosis



(A) Electrocardiogram showing low voltage, atrial fibrillation, and slow ventricular response. (B) Echocardiogram demonstrating concentric hypertrophy and atrial enlargement concerning for cardiac amyloidosis. (C) Pathologic examination results demonstrating pale amyloidosis in myocyte tissue, H&E stain (original magnification, 10x). (D) Apple green birefringence observed under polarized light indicating presence of amyloidosis, Congo red stain (original magnification, 20x).

TABLE 1 Summary of History, Diagnostic Testing, and Follow-Up for 3 Patients With diagnoses of Coexisting Light Chain and Transthyretin Amyloid Cardiomyopathy on Endomyocardial Biopsy

Factor	Patient 1	Patient 2	Patient 3
Demographics			
Age, y	83	90	85
Sex	Male	Male	Male
Race	African-American	Caucasian	African-American
Comorbidities, cardiac	Hypertension, severe AS s/p TAVR	Atrial fibrillation, hypertension, moderate AS	Hypertension
Comorbidities, noncardiac	Bilateral CTS, lumbar spinal stenosis	Hypothyroidism	Bilateral CTS, chronic kidney disease
TTR pathogenic mutation	None	None	Val122Ile
Diagnostic data			
NT-proBNP (pg/mL)	1,532	5,798	5,845
Troponin I (ng/dL)	0.09	0.06	0.05
Creatinine (mg/dL)	1.1	0.9	2.4
Hemoglobin (g/dL)	12.9	11	12.6
Serum κ (mg/L)	993	731.5	122.7
Serum λ (mg/L)	8.8	23.3	99.8
κ/λambda ratio	113	31.39	1.23
SIFE	IgG monoclonal gammopathy	IgG monoclonal gammopathy	No monoclonal gammopathy
Bone marrow biopsy	Plasma cells involving 30% of bone marrow, with κ light chain restriction	Plasma cells involving <10% of bone marrow, with κ light chain restriction	N/A
Echocardiogram	EF 60%-65%, moderate LVH, biatrial enlargement	EF 70%-75%, small LV cavity size, moderate LVH, severe biatrial enlargement, moderate AS	EF 50%-55%, moderate LVH, GLS -12.1% with apical sparing, severely dilatated left atrium, small pericardial effusion,
Follow-up			
Treatment	Tafamidis, lenalidomide, daratumumab	Tafamidis, daratumumab	N/A, Lost to follow-up
Outcome	Alive at 1 year after presentation, NYHA class II	Alive at 2 years after presentation, NYHA class II	Deceased 6 months after presentation

AS = aortic stenosis; CTS = carpal tunnel syndrome; EF = ejection fraction; GLS = global longitudinal strain; LV = left ventricle; LVH = left ventricular hypertrophy; N/A = not applicable; NYHA = New York Heart Association; s/p = status post; TAVR = transcatheter aortic valve replacement.

He underwent endomyocardial biopsy, and examination of a biopsy specimen showed AL (κ) and wtATTR amyloid deposition on mass spectrometry. He was started on daratumumab for AL-CM and tafamidis for ATTR-CM and continues to do well 2 years after initial presentation.

PATIENT 3

An 85-year-old African-American man with a history of chronic kidney disease, hypertension, and bilateral carpal tunnel syndrome presented with acute decompensated HF. Electrocardiogram revealed atrial flutter with variable block. Echocardiogram was significant for an EF of 50% to 55%, moderate LVH, global longitudinal strain of −12.1% with apical sparing, severely dilatated left atrium, and small pericardial effusion. Serum free κ and λ light chains were elevated (122.7 mg/L and 99.8 mg/L, respectively), with a ratio of 1.23. Serum immunofixation showed no monoclonal gammopathy. He underwent endomyocardial biopsy, and examination of the biopsy specimens showed both AL (κ) and hATTR (Val122Ile) mutant peptide deposition by mass spectrometry. Owing to the absence of a monoclonal gammopathy, there was concern that the mass spectrometry specimen was contaminated. However, upon detailed review, both proteins were confirmed to be present. Initiation of therapy with daratumumab and tafamidis was planned; however, he was unable to come to follow-up care and died prior to starting therapy.

DISCUSSION

We present 3 cases of coexisting AL and ATTR-CM, adding to the limited reports of this rare entity. One series describes 2 patients presenting with volume overload later found to have AL and ATTR-CM; however, both patients died shortly after diagnosis, and no available treatments were available for ATTR-CM at the time.[2] Another report describes a single

patient who initially received a diagnosis of ATTR-CM but later experienced worsening symptoms and was found to have AL-CM on second endomyocardial biopsy.[3] Our cases are unique in that endomyocardial biopsy was pursued despite a diagnosis of MM with disease-modifying treatment for AL-CM already initiated (patient 1) and treatment was implemented for both AL and ATTR-CM with favorable outcome. Our series highlights that early recognition of multiple amyloid subtypes is essential to guide treatment, especially now that disease-modifying therapies are available for ATTR-CM.[4]

Cardiac amyloidosis may initially be suspected on the basis of certain cardiac and noncardiac "red flags" (Table 2). Although AL and ATTR-CM can overlap regarding noncardiac manifestations of disease, macroglossia, submandibular gland enlargement, coagulopathy, and periorbital purpura more commonly associate with AL-CM, whereas bilateral carpal tunnel syndrome, spinal stenosis, hip/knee replacement, and peripheral neuropathy have been more commonly described with ATTR-CM.[1,5,6] Recognition of these unique features of AL and ATTR-CM may allow one to establish a higher pretest probability for 1 disease entity. For example, with patient 1, despite a diagnosis of MM, suspicion remained high for ATTR-CM because of the patient's advanced age, severe aortic stenosis, bilateral carpal tunnel syndrome, and spinal stenosis.

The contemporary diagnostic algorithm for ATTR-CM has shifted to a noninvasive approach in patients who have normal light chain test results.[7] We highlight the ongoing role of endomyocardial biopsy for diagnosis of ATTR-CM.[1] In particular, in patient 1, the utility of endomyocardial biopsy was initially unclear because of the diagnosis of MM already under treatment, and in whom analysis of a tissue biopsy specimen confirming AL-CM would not have changed the underlying approach to disease-modifying treatment. However, because of suspicion for concomitant ATTR-CM, endomyocardial biopsy was pursued, which led to detection of wtATTR-CM and initiation of tafamidis. Additional indications for endomyocardial biopsy when ATTR-CM is detected is the detection of a monoclonal gammopathy or concern for a false-negative scintigraphy scan.[1,7] Regarding the former, this is because AL-CM cannot be ruled out in the presence of a monoclonal gammopathy and is associated with a false-positive nuclear scintigraphy scan in ≤20% of cases.[1,8] With advanced age, there is the possibility of incidental, rather than pathologic, detection of wtATTR. As such, communication with the pathology department about the burden of amyloid by subtype can be helpful to guide treatment decisions. In our cases, after risk/benefit discussions with our patients, we elected to treat for ATTR-CM given the progressive nature of the disease.

TABLE 2 Cardiac and Noncardiac "Red Flags" Seen With Cardiac Amyloidosis

Cardiac clues
Intolerance to standard heart failure GDMT (ie, β-blockers or RAAS inhibitors)
Resolving hypertension
HFpEF diagnosis in the absence of HFpEF risk factors (ie, obesity, hypertension)
Unexplained atrioventricular block
Persistent low-level troponin elevation
Disproportionate voltage to LV mass on electrocardiogram
Echocardiogram: unexplained LVH (ie, present despite well-controlled hypertension), RVH, small to normal LV cavity size, biatrial enlargement, aortic stenosis, trace pericardial effusion, apical sparing pattern on global longitudinal strain
cMRI: LV subendocardial or diffuse LGE, atrial LGE, increased ECV, decreased T1 time, increased intra-atrial septal thickness
Noncardiac clues
Neurologic: peripheral neuropathy (sensory symptoms), autonomic neuropathy (orthostatic hypotension)
Orthopedic: bilateral carpal tunnel syndrome, lumbar spinal stenosis, multiple prior joint arthroscopies, biceps tendon rupture
Gastrointestinal: diarrhea, constipation, gastroparesis
Hematologic: coagulopathy (factor X deficiency), periorbital purpura
Other: macroglossia, submandibular gland enlargement

cMRI = cardiac MRI; ECV = extracellular volume; GDMT = guideline directed medical therapy; HFpEF = heart failure with preserved ejection fraction; LGE = late gadolinium enhancement; LV = left ventricle; LVH = left ventricle hypertrophy; RAAS = renin angiotensin aldosterone system; RVH = right ventricle hypertrophy.

A multidisciplinary approach between the cardiology, hematology/oncology, and pathology departments is essential to diagnose and manage cardiac amyloidosis. After detection of amyloidosis by Congo red staining on tissue biopsy specimens, mass spectrometry remains the gold standard for identification of the amyloid precursor protein. This is particularly important in cases where multiple amyloid subtypes are suspected, or when a monoclonal gammopathy is present but suspicion for ATTR-CM remains high. Communication with a pathologist and a center with mass spectrometry capability is essential for accurate identification of protein subtype in cardiac amyloidosis.

CONCLUSIONS

Our case series adds to the limited literature on detection of concomitant AL and ATTR-CM. Whereas the current diagnostic algorithm for cardiac amyloidosis does allow for identification of coexisting AL and ATTR-CM, there are circumstances where endomyocardial biopsy may ordinarily be deferred yet should be considered (ie, multiple myeloma) if

there is suspicion for ATTR-CM to facilitate accurate diagnosis and optimize disease-related outcomes.

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