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MINI-FOCUS ISSUE: HEART FAILURE

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Biopsy Evidence of Sequential Transthyretin and Immunoglobulin Light-Chain Cardiac Amyloidosis in the Same Patient

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ABSTRACT

Currently adopted diagnostic flow charts consider transthyretin and light-chain cardiac amyloidosis as mutually exclusive. Here, we report for the first time, to our knowledge, the demonstration of a biopsy-proven dual pathology in an 80-year-old man with sequential development of both wild-type transthyretin amyloidosis and light-chain cardiac amyloidosis cardiomyopathy over a 3-year timespan. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:450–4)

HISTORY OF PRESENTATION

In May 2016, an 80-year-old man presented to our clinic because of worsening dyspnea (New York Heart Association functional class II). At presentation, his blood pressure was 130/80 mm Hg, and his heart rate was 76 beats/min. Physical examination findings were unremarkable.

MEDICAL HISTORY

The patient had a history of hypertension. In February 2016, an immunoglobulin (Ig) M kappa monoclonal gammopathy of undetermined significance was found on a routine blood test prescribed by his general practitioner.

DIFFERENTIAL DIAGNOSIS

Based on age, comorbidities, and clinical presentation, the most plausible diagnosis seemed to be a

LEARNING OBJECTIVES

- To understand that cardiac amyloidosis is an important cause of heart failure and that the correct identification of the amyloidosis subtype is crucial for the initiation of potentially life-saving treatments.
- To demonstrate that transthyretin (ATTR) and light-chain (AL) amyloidosis, although considered as mutually exclusive by currently adopted diagnostic flow charts, can rarely coexist.
- To highlight that development of AL amyloidosis could be suspected when patients with established ATTR cardiomyopathy experience clinical deterioration associated with other biohumoral or imaging red flags for AL amyloidosis.

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decompensated heart failure (HF), possibly due to an ischemic event or a cardiomyopathy.

INVESTIGATIONS

A transthoracic echocardiogram showed increased left ventricular (LV) wall thickness, mildly reduced LV ejection fraction (LVEF) of 52%, and grade 1 diastolic dysfunction (**Figure 1**, Video 1). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 460 ng/l, and high-sensitivity cardiac troponin T (hs-cTnT) was 24 ng/l. Kappa and lambda light-chain levels were 377 and 106 mg/dl, respectively (kappa/lambda ratio: 3.55) (**Table 1**). Based on these results, the patients underwent a diagnostic workup for cardiac amyloidosis (CA). Cardiac magnetic resonance (CMR) showed increased LV mass index (106 g/m^2) and midwall late gadolinium enhancement involving the basal and mid segments of the anterior interventricular septum (**Figure 1**, Video 2). ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) scintigraphy showed mild myocardial uptake (Perugini score: 1) (**Figure 1**). Coronary angiogram was unremarkable. Endomyocardial biopsy specimens showed positive interstitial Congo Red staining and colocalized positive transthyretin immunostaining, with negative kappa and lambda light-chain immunostaining (**Figure 2**). No *TTR* variant was identified at genetic analysis. A diagnosis of early-stage wild-type transthyretin amyloidosis (ATTR) was established. Treatment with valsartan and spironolactone was initiated for better management of pre-existing hypertension and for the presence of symptoms of HF; furosemide was introduced for volume/edema control. In April 2018, ^{99m}Tc-HMDP scintigraphy revealed a moderate cardiac uptake (Perugini score: 2), with intense septal and inferior wall uptake.

In January 2019, the patient started complaining of worsening dyspnea (New York Heart Association functional class III) and presented with mild bilateral ankle edema, increased NT-proBNP (2586 ng/l) and hs-cTnT (48 ng/l). Waldenström macroglobulinemia was diagnosed, with kappa and lambda light-chains level

ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light-chain amyloidosis

ATTR = transthyretin amyloidosis

CA = cardiac amyloidosis

CMR = cardiac magnetic resonance

HF = heart failure

hs-cTnT = high-sensitivity cardiac troponin T

Ig = immunoglobulin

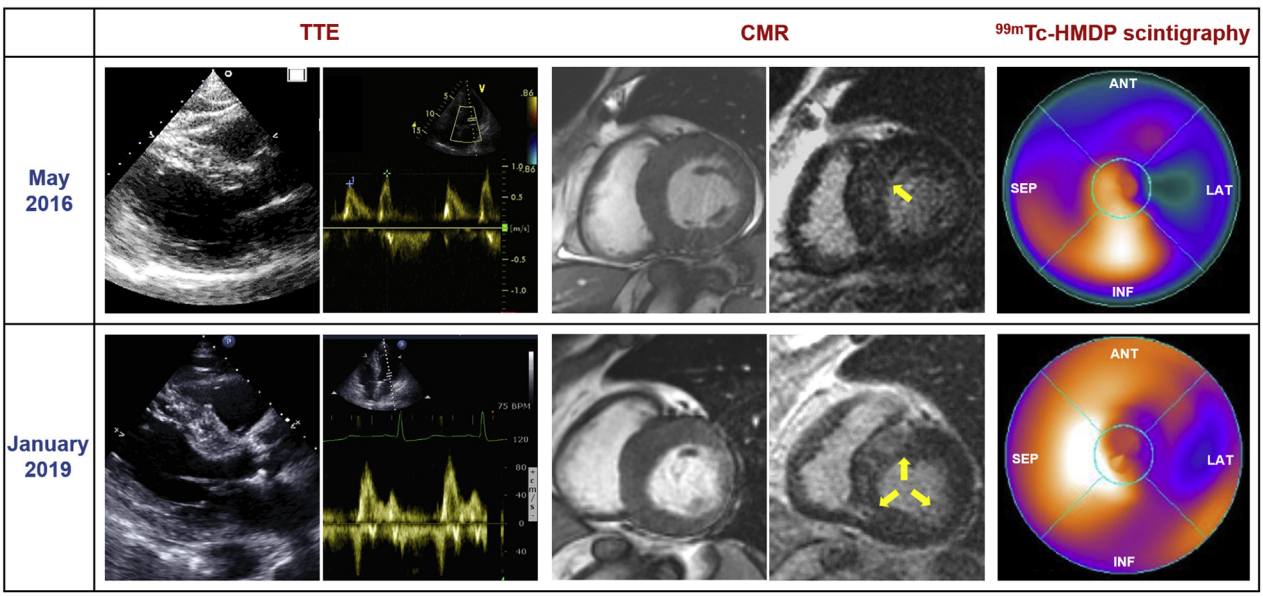
LV = left ventricular

LVEF = left ventricular ejection fraction

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

^{99m}Tc-HMDP = ^{99m}Tc-hydroxymethylene diphosphonate

FIGURE 1 Imaging Features at Baseline and After 3 Years



(Left) Transthoracic echocardiography (TTE) (parasternal long-axis view and transmitral Doppler) showing left ventricular pseudohypertrophy and change in transmitral Doppler from impaired relaxation to restrictive pattern after 3 years. **(Middle)** Cardiac magnetic resonance (CMR) (pre-contrast and late post-contrast short-axis view) demonstrating extension of late gadolinium enhancement (yellow arrows) between the 2 diagnostic workups. **(Right)** ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) scintigraphy (bull's eye view) at both the first and second diagnostic workups highlighting progression of myocardial uptake from circumscribed inferior wall uptake to intense septal and inferior wall uptake. Bull's eye depicts relative myocardial tracer uptake: the apparent decrease in inferior wall uptake at follow-up ^{99m}Tc-HMDP scintigraphy is due to lower intensity relative to the marked uptake of the septal regions. ANT = anterior; INF = inferior; LAT = lateral; SEP = septal.

TABLE 1 Biohumoral Findings at the Time of the 2 Hospital Admissions

	May 2016	January 2019	Reference Value
Blood			
NT-proBNP, ng/l	460	2,586	<125
hs-cTnT, ng/l	24	48	<14
Creatinine, mg/dl	0.84	1.06	<1.30
IgM, mg/dl	1,330	1,450	40–230
Kappa light chain, mg/dl	377	305	170–370
Lambda light chain, mg/dl	106	73	90–120
Kappa/lambda ratio	3.55	4.18	
Urine			
Kappa light chain, mg/dl	7.16	NA	<1.00
Lambda light chain, mg/dl	0.94	NA	<0.50
Kappa/lambda ratio	7.62	NA	

hs-cTnT = high-sensitivity cardiac troponin T; Ig = immunoglobulin; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

at 305 and 73 mg/dl, respectively (kappa/lambda ratio: 4.18) (**Table 1**). Echocardiogram showed decreased LVEF (40%) as well as mild pericardial and bilateral pleural effusion (**Figure 1**, Video 3). CMR demonstrated an extension of midwall late gadolinium enhancement, now involving the basal to mid segments of the anterior and inferior interventricular septum and the mid portion of the inferior LV wall, with no change in LV mass index (107 g/m^2) (**Figure 1**, Video 4). ^{99m}Tc-HMDP scintigraphy was repeated (**Figure 1**) and was unchanged in comparison with the previous follow-up scintigraphy scan from April 2018. An endomyocardial biopsy was repeated, showing intense transthyretin and kappa light-chain immunostaining, with negative lambda staining (**Figure 2**). A diagnosis of dual CA (ATTR and Ig light-chain amyloidosis [AL]) was established.

MANAGEMENT

A hematologic treatment with oral chlorambucil and prednisone was initiated on top of a background cardioactive treatment.

DISCUSSION

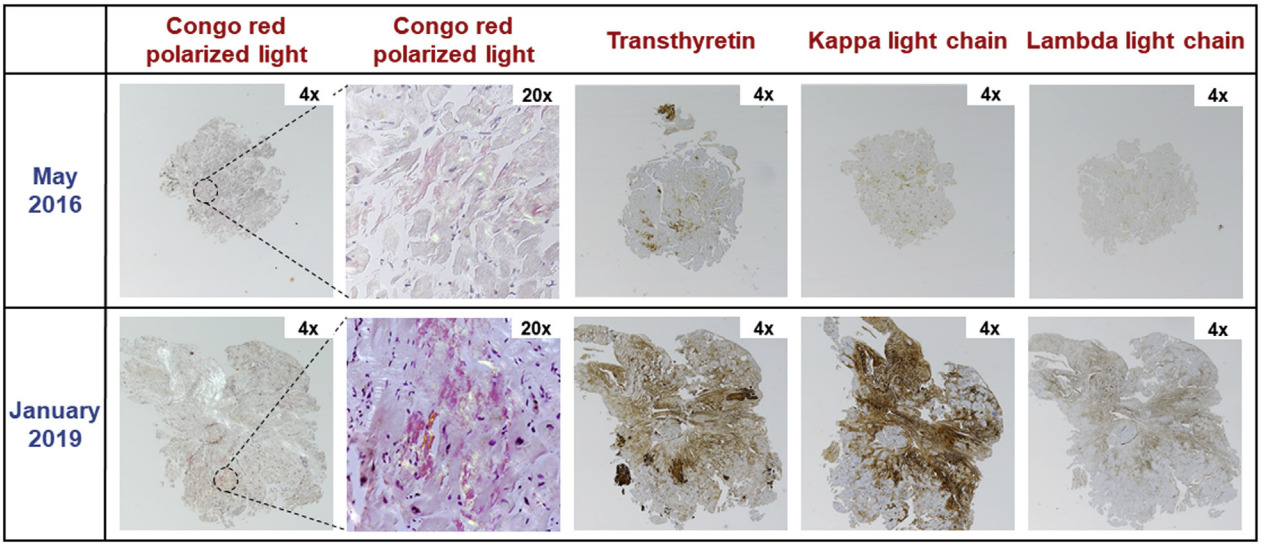
CA is increasingly recognized as a cause of HF. The 2 most common forms, ATTR and AL, are considered as mutually exclusive by the currently adopted diagnostic flow charts. The elevation of circulating markers of cardiac damage, together with the combined electrocardiographic and echocardiographic evidence of myocardial pseudohypertrophy should prompt the suspicion of CA, which can be finally confirmed by means of the histological demonstration of amyloid deposits or, in selected cases of ATTR cardiomyopathy, by myocardial uptake at nuclear scintigraphy with bone-seeking radiotracer (1). The amyloid subtype largely influences clinical presentation, management, and outcome. A timely diagnosis is therefore crucial for the initiation of life-saving treatments, given the current availability of different chemotherapy regimens and, in selected cases, of autologous bone marrow transplant for AL amyloidosis, as well as the recent development of drugs targeting specific steps of the amyloidotic cascade in ATTR amyloidosis (2).

The identification of different types of amyloidosis in the same patient is anecdotal. In a recent case series from the Mayo Clinic, evidence of dual amyloidosis, as either 2 distinct amyloid types infiltrating different tissues or 2 amyloid types within the same tissue specimen, has been demonstrated by mass spectrometry in 9 out of 1,094 consecutive patients with amyloidosis (2). In most cases, the identification of a second amyloid type was an incidental finding during the initial diagnostic workup for a specific amyloidosis (usually AL amyloidosis) and did not affect the subsequent clinical management (3). Only 2 cases of sequential diagnosis of dual amyloidosis have been reported so far: 1) a 31-year-old woman with renal deposition of serum amyloid A who was later diagnosed with AL amyloidosis (bone marrow and duodenum biopsy samples were both positive for lambda light-chain fibrils) after evaluation for weight loss and bleeding (4); and 2) a 70-year-old man with AL amyloidosis (holding the Val122Ile mutation) who showed infiltration of both Ig light-chain and mutated transthyretin in a second bone marrow biopsy performed 11 years after the first (3).

As for cardiac dual amyloidosis, Bergström et al. (5) first described the coexistence of 2 different amyloid deposits, due to transthyretin and apolipoprotein IV, in autoptic cardiac specimens from a 92-year-old man, and Liepnieks and Benson (6) reported the concomitant deposition of transthyretin and lambda light chains in myocardial autoptic samples from a patient with restrictive cardiomyopathy. Concomitant ATTR and AL cardiac amyloidosis have also been demonstrated by mass spectrometry in a case report by Mahmood et al. (7), in 2 patients by Sidiqi et al. (3), and in 2 other patients by Donnelly et al. (8).

To our knowledge, this is the first description of a biopsy-proven sequential development of cardiac ATTR and AL amyloidosis in a patient presenting with signs and symptoms of HF. Of note, the presence of HF symptoms at first hospital admission was, together with mild cardiac uptake at ^{99m}Tc-HMDP scintigraphy, a disease red flag that prompted us to complete the diagnostic workup with an endomyocardial biopsy, which allowed the diagnosis of ATTR cardiomyopathy. The underlying kappa protein,

FIGURE 2 Endomyocardial Biopsies at the Time of the 2 Hospital Admissions



Congo Red staining, *transthyretin, and* kappa and lambda light-chain immunostaining from endomyocardial biopsies performed at the first and second diagnostic workups. An intense kappa chain staining can be observed in the specimen from the second biopsy but not in the first.

which less commonly leads to a diagnosis of amyloidosis, and the unusual occurrence of myocardial involvement in IgM-associated amyloidosis are further elements of peculiarity. Differently from previous cases of cardiac dual amyloidosis, the diagnosis of the second amyloid type was not incidental, because it occurred after clinical and functional worsening and evolution of the hematologic disorder. Because the gold standard liquid chromatography/mass spectrometry was not available at our center, the characterization of amyloid fibrils was achieved by immunohistochemistry, revealing a strong positivity for both transthyretin and Ig kappa light chain. A faint balanced reactivity for both kappa and lambda light chains was present in the first endomyocardial biopsy, which is usually representative of a nonspecific background signal.

As a further peculiarity, ^{99m}Tc-HMDP scanning was used to track disease progression in this case. ^{99m}Tc-HMDP scintigraphy is repeated during the follow-up in selected patients at our center, particularly when initial cardiac uptake is mild. However, ^{99m}Tc-HMDP scintigraphy is currently recommended only for diagnostic purposes in ATTR amyloidosis, and disease surveillance through serial examinations is not an evidence-based standard of care.

Although uncommon, the possible development of AL amyloidosis in patients with established ATTR should be suspected when other biohumoral or imaging red flags are identified, because it may prompt the initiation of targeted treatment and improve patient outcome (1).

FOLLOW-UP

At the latest follow-up visit, in February 2020, the patient was asymptomatic and without signs of HF. Chemotherapy treatment had yielded a partial hematologic (reduction in kappa/lambda ratio to 1.96) and cardiac response (increase in LVEF up to 56%).

CONCLUSIONS

ATTR and AL amyloidosis can develop subsequently in the same patient. This possibility should be considered when patients with ATTR cardiomyopathy experience clinical deterioration associated with other biohumoral or imaging red flags for AL amyloidosis.

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KEY WORDS AL amyloidosis, ATTR amyloidosis, cardiac amyloidosis

APPENDIX For supplemental videos, please see the online version of this paper.