JACC: CARDIOONCOLOGY VOL. 6, NO. 4, 2024

CLINICAL CASE CHALLENGES

Light-Chain Pericardial Amyloidosis Emerging Alongside Variant Transthyretin Cardiac Amyloidosis

Alexander H. Gunn, MD,[a] Johana Fajardo, DNP,[a,b] Louis Dibernardo, MD,[c] Carolyn Glass, MD,[c] Fawaz Alenezi, MD,[a,b] Ravi Karra, MD,[a,b,c] Ellen D. McPhail, MD,[d] Cristiana Costa Chase, DO,[a,e] Michel G. Khouri, MD[a,b]

Cardiac amyloidosis (CA) is caused by extracellular deposition of amyloid fibrils composed of misfolded proteins within cardiac tissues, leading to restrictive cardiomyopathy. The majority of CA cases are caused by amyloid proteins derived from transthyretin (leading to transthyretin cardiac amyloidosis [ATTR-CA]), which is predominantly synthesized by hepatocytes, or from immunoglobulin light-chain amyloidosis (AL-CA) typically produced by clonal plasma cells.[1] Transthyretin amyloidosis (ATTR) can be further classified as secondary to inherited structurally destabilizing variants in the transthyretin gene (variant transthyretin amyloidosis [ATTRv]) or the acquired unstable wild-type transthyretin protein (wild-type transthyretin amyloidosis [ATTRwt]). Historically, diagnosis included histologic confirmation of amyloid in the affected organ(s) using Congo red staining, with fibril typing suggested by immunohistochemistry and confirmed with proteomic analysis by laser microdissection with liquid chromatography-tandem mass spectrometry (LC-MS/MS).[1] Radioisotope myocardial uptake on bone scintigraphy now permits nontissue diagnosis of ATTR-CA in patients without monoclonal gammopathies. Diagnostic pathways for AL-CA and ATTR-CA algorithmically diverge but are not mutually exclusive, with comprehensive assessment critical for timely initiation of treatment appropriate to subtype.[1]

The presence of multiple precursor proteins for CA in an individual patient is exceedingly rare and limited to case reports/series of co-occurring distinct amyloid subtypes detected at either single or separate anatomic site(s). To our knowledge, a total of 8 cases of CA with distinct subtypes diagnosed concurrently at the initial work-up (n = 6) or autopsy (n = 2) have been reported, all with lambda light-chain amyloidosis (ALλ) and ATTRwt.[2-7] Separately, in AL-CA patients, the presence of transthyretin variants[8] and extracardiac ATTRv deposition[3] without variant transthyretin cardiac amyloidosis (ATTRv-CA) have been reported. Here, we present the first case (to our knowledge) of CA with endomyocardial biopsy evidence of ATTRv and, subsequently, after clinical deterioration despite ATTR-CA disease-modifying therapy, evidence of kappa light-chain amyloidosis (ALκ) co-occurring with ATTRv in the same pericardial microdissection.

CASE

A 71-year-old man with a history of coronary artery disease and bilateral carpal tunnel syndrome presented to the emergency department with several weeks of worsening dyspnea with mild exertion, bilateral lower extremity edema, and orthopnea in December 2021. He was hospitalized for acute heart failure (HF) with NYHA functional class III symptoms and treated with intravenous diuretic therapy. A transthoracic echocardiogram (TTE) demonstrated left ventricular ejection fraction of 60%, grade 2 diastolic dysfunction, and moderate

From the [a]Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA; [b]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA; [c]Department of Pathology, Duke University School of Medicine, Durham, North Carolina, USA; [d]Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, Rochester, Minnesota, USA; and the [e]Division of Hematologic Malignancies and Cell Therapy, Duke University School of Medicine, Durham, North Carolina, USA.

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.

Manuscript received November 21, 2023; revised manuscript received April 2, 2024, accepted April 2, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.04.002

pericardial effusion without tamponade physiology. B-type natriuretic peptide (159 pg/mL, reference <100 pg/mL) and high-sensitivity troponin I (43 ng/L, reference <20 ng/L) levels were mildly elevated.

In February 2022, the patient had an electrocardiogram notable for low voltage and first-degree atrioventricular block. A repeat TTE noted severe concentric left ventricular hypertrophy; a follow-up cardiac magnetic resonance scan confirmed the TTE findings and noted a diffuse ventricular hyperenhancement pattern with elevated native T1 mapping (1,541 milliseconds) and extracellular volume expansion (65%) consistent with CA. Monoclonal protein studies showed immunoglobulin G-κ monoclonal protein on serum immunofixation electrophoresis and immunoglobulin G-κ monoclonal protein and κ-free light chains (FLCs) on urine immunofixation electrophoresis with elevated κ-serum FLC concentration (9.71 mg/dL, reference 0.33-1.94 mg/dL) and κ/λ ratio (9.06, reference 0.26-1.65).

After referral to our institution in April 2022, endomyocardial biopsy (Figure 1) was performed and demonstrated moderate amyloid deposition in a mixed nodular and perimyocytic pattern. Subsequent LC-MS/MS detected exclusively ATTR-type peptides, including ATTR peptides with an amino acid sequence abnormality consistent with the V122I (p.Val142Ile) allelic variant; serum TTR genotyping confirmed a heterozygous V122I allelic variant. Tafamidis was started in June 2022 for a diagnosis of ATTRv-CA with HF.

The presence of monoclonal gammopathy prompted a hematology evaluation in May 2022. Subsequent bone marrow biopsy (Figure 1) showed amyloid deposition by Congo red stain and ∼10% abnormal plasma cells in 30% cellular bone marrow; LC-MS/MS exclusively detected ALκ-type peptides. The patient reported dysphagia and weight loss in the context of rising κ-serum FLC concentrations leading to clinical suspicion of organ involvement with amyloid light-chain (AL) amyloidosis; however, biopsy specimens from endoscopies in May 2022 (stomach) and November 2022 (esophagus, stomach, and duodenum) and from abdominal skin in August 2022 were negative by Congo red staining. To that point, lacking evidence of organ involvement with AL amyloidosis, hematology surveillance was continued for a smoldering myeloma diagnosis.

ABBREVIATIONS AND ACRONYMS

AL = amyloid light chain

ALκ = kappa light-chain amyloidosis

ALλ = lambda light-chain amyloidosis

AL-CA = light-chain cardiac amyloidosis

ATTR = transthyretin amyloidosis

ATTR-CA = transthyretin cardiac amyloidosis

ATTRv = variant transthyretin amyloidosis

ATTRv-CA = variant transthyretin cardiac amyloidosis

ATTRwt = wild-type transthyretin amyloidosis

CA = cardiac amyloidosis

FLC = free light chain

HF = heart failure

LC-MS/MS = liquid chromatography-tandem mass spectrometry

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

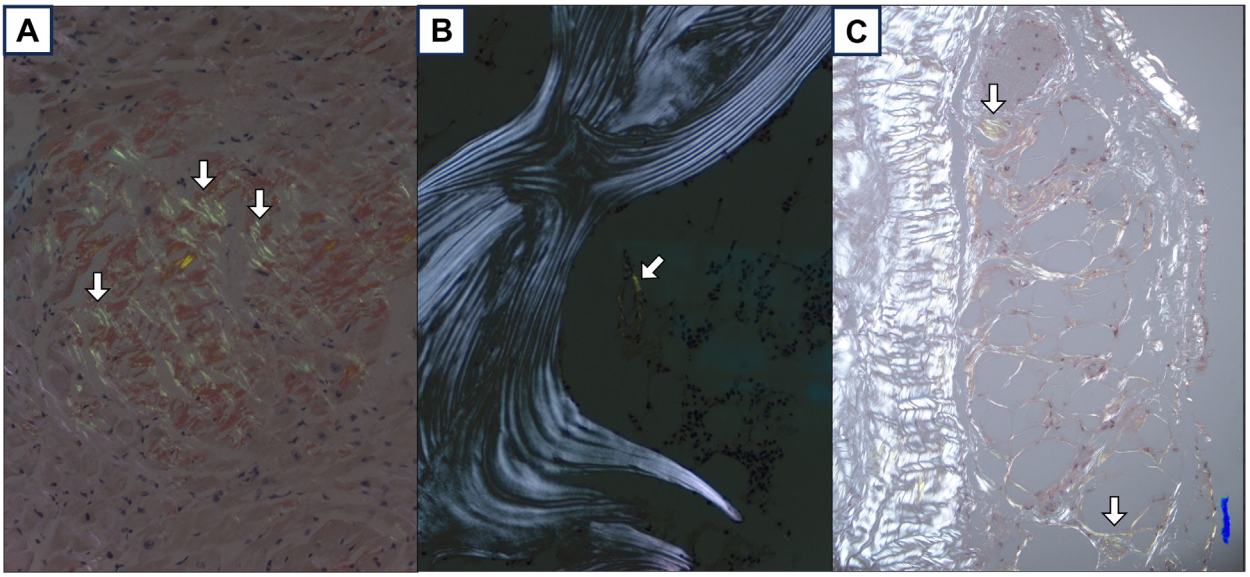
RVSP = right ventricular systolic pressure

TTE = transthoracic echocardiogram

By Fall 2022, the patient's HF symptoms and functional class (NYHA functional class II) had improved. However, in January 2023, the patient reported worsening lower extremity edema, dyspnea, and early satiety. Intensified loop diuretic agents and empagliflozin initiation did not attenuate a deterioration back to NYHA functional class III. Repeat TTE demonstrated interval left ventricular ejection fraction decline to 45%, increased pericardial effusion with a plethoric inferior vena cava, and higher tricuspid regurgitation velocity and estimated right ventricular systolic pressure (RVSP) at 3.5 m/s and 69 mm Hg (previously 2.5 m/s and 36 mm Hg, respectively). Laboratory bloodwork from May 2022 to March 2023 revealed increasing N-terminal pro-B-type natriuretic peptide (NT-proBNP), proteinuria, creatinine, and κ/λ ratio; prealbumin increased appropriately on tafamidis (Table 1).

The patient underwent subxiphoid pericardial window creation in February 2023 for acute HF with concern for progressive effusion-related extracardiac compression in addition to underlying ATTRv-related restrictive physiology. Thereafter, functional class (NYHA functional class II), renal function, loop diuretic requirements, and TTE-derived estimated RVSP (40 mm Hg) improved. Histologic examination of the pericardium demonstrated amyloid deposition in the pericardial tissue (fibrous and adipose) and small vessels, which was confirmed by Congo red stain (Figure 1). LC-MS/MS detected a predominant component of ALκ-type peptides and a minor component of ATTR-type peptides, including ATTR peptides consistent with V122I allelic variant. Antiplasma cell therapy with cyclophosphamide-bortezomib-dexamethasone and daratumumab was started for systemic ALκ amyloidosis. Relative to baseline levels of serum FLC (κ = 13.95 mg/dL, λ = 1.73 mg/dL) and NT-proBNP (3,044 pg/mL) at cyclophosphamide-bortezomib-dexamethasone and daratumumab initiation in April 2023, there was a very good partial hematologic response (ie, κ-λ FLC difference <4 mg/dL) and cardiac partial response (ie, 57% NT-proBNP reduction) by February 2024 (Table 1).

FIGURE 1 Congo Red Staining of Endomyocardium, Bone Marrow, and Pericardium Biopsies



Apple-green birefringence on polarized light microscopy of Congo red-stained tissues from (A) the endomyocardium, (B) bone marrow, and (C) pericardium. Marker arrows denote areas of amyloid deposition.

DISCUSSION

This report presents a case with unique features of coexistent ATTRv-CA and pericardial ALκ amyloid deposition with biopsy evidence of evolution from pure ATTR-CA in the endomyocardium to hybrid ATTR/AL deposition in the pericardium. For concurrent amyloid subtypes, only the dual presence of ATTRwt-CA and ALλ-CA has been documented previously.[2-7] In a case series of 2 patients by Donnelly et al,[4] along with individual case reports by Mahmood et al[2] and Moriyama et al,[5] codeposition was identified during an initial

TABLE 1 Evolution of Clinical and Biomarker Findings

	March-May 2022	January-March 2023	February 2024	Reference Range
Clinical scenario	Pretafamidis	Prepericardial Window	Tafamidis and Dara-CyBorD	
Blood				
NT-proBNP, pg/mL	1,426	2,834	1,296	≤225
hsTnI, ng/L	61	108	–	<20
Creatinine, mg/dL	1.1	1.9	1.5	<1.3
eGFR, mL/min/1.73 m^2	72	37	49	
Prealbumin, mg/dL	12.8	27.9	27.0[a]	18-45
Kappa light chains, mg/dL	9.49	12.46	2.33	0.33-1.94
Lambda light chains, mg/dL	1.11	1.26	0.90	0.57-2.63
Kappa/lambda ratio	8.55	9.89	2.59	0.26-1.65
Modified BMI[b]	1,267.6	1,098.3	1,200.4	
Urine				
Total protein, 24-h urine, mg	329	975	400[a]	<229/24 h
Diuretic therapy				
Torsemide dose, mg/d	30	60	20	

[a]Presented value is from late 2023. [b]Modified BMI = BMI (kg/m^2) multiplied by serum albumin (g/L).

BMI = body mass index; Dara-CyBorD = daratumumab and bortezomib-cyclophosphamide-dexamethasone; eGFR = estimated glomerular filtration rate; hsTnI = high-sensitivity troponin I; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

comprehensive assessment of amyloidosis. Sidiqi et al[3] retrospectively identified 2 cases in which cardiac specimens showed pure AL and hybrid AL/ATTR. Liepnieks and Benson[6] and Shintani-Domoto et al[7] identified individual cases on myocardial autopsy samples. Among 6 patients alive at the time of concurrent diagnoses, 4 received treatment for AL-CA alone or died before treatment could be initiated;[2-4] 1 patient had unspecified dual therapy for AL-CA and ATTR-CA,[3] and 1 patient died before starting AL treatment after 5 months of tafamidis and worsening proteinuria.[5]

Although myocardial involvement is nearly ubiquitous in V122I ATTRv amyloidosis, tissue tropism in systemic AL amyloidosis is variable. Light-chain variable region genes appear to influence AL amyloidogenesis and predilection of organ deposition.[9] However, clinical light-chain variable region genotype testing is not routinely pursued for smoldering myeloma and has unknown utility for discerning AL amyloid deposition among distinct tissues within the same organ. In our patient, a worsening HF syndrome after the diagnosis and treatment of ATTRv-CA prompted additional investigation that led to the identification of pericardial AL amyloid deposition, suggesting that either: 1) the onset of ALκ pericardial deposition naturally lagged behind ATTRv-CA; or 2) ALκ pericardial deposition was already coexistent with ATTRv-CA, but differing relative cardiac tissue tropism meant endomyocardial biopsy alone was insufficient.

The timing of AL pericardial involvement in this case cannot be determined precisely. Deposition of ALκ-type amyloid was not initially detected outside the bone marrow on endomyocardial or multisite extracardiac biopsies, which generally have higher yield for AL amyloidosis than ATTR amyloidosis.[1] This suggests a delayed onset of systemic AL amyloidosis; notably, the typical course in AL amyloidosis patients with persistence of culprit light-chain proteins or prolonged survival includes eventual cardiac involvement.[1] This proposed timeline of events is supported by observed worsening of proteinuria in the interval between ATTRv-CA diagnosis and the detection of ALκ amyloid deposits in the pericardium and by the patient's overall clinical course. Specifically, his symptomatic decline and enlarging pericardial effusion on tafamidis; subsequent prompt clinical response (ie improved symptoms, renal function, and echocardiographic indexes [eg, RVSP]) after the pericardial window; and, thereafter, the hematologic and organ response on antiplasma cell therapy highlight that AL amyloid involvement of the pericardium had both hemodynamic significance and an important role as a confirmatory marker of systemic AL amyloidosis.

It is possible that limitations in the sensitivity of the initial endomyocardial tissue sampling contributed to delayed identification of systemic AL amyloidosis. In the case reported by Mahmood et al,[2] ATTR and AL amyloid proteins were found in distinct areas within the endomyocardial tissue,[2] raising the possibility that AL amyloid proteins were not initially detected because of inadequate sampling of the congophilic tissue within the endomyocardium. In our case, comprehensive microdissection and subsequent mass spectrometry on all involved anatomical compartments made it unlikely that AL amyloid deposits were missed on the original endomyocardial sample. Notably, the incremental diagnostic yield of the pericardial tissue was unanticipated because the presence of a pericardial effusion has not effectively discriminated between AL-CA and ATTR-CA in previous studies[8,10] and directed pursuit away from a repeat endomyocardial biopsy that could have potentially confirmed AL-CA.

Although the scenario that unfolded in our patient is uncertain, this case highlights the importance of allowing for the possibility of multiple pathologies during CA evaluation. Moreover, it emphasizes that despite evidence of ATTR-type amyloid deposits within the involved organ (ie, cardiac), histologic evaluation for amyloidosis should not cease if AL amyloidosis has not been ruled out in a patient with abnormal monoclonal protein testing. At a minimum, such patients need a hematology consultation[1] and a low threshold for bone marrow biopsy with potential consideration of sampling at other sites, particularly if systemic involvement is clinically suspected.

CONCLUSIONS

This report presents the first case of V122I ATTRv-CA co-occurring with pericardial ALκ amyloid deposition and highlights the importance of persistent comprehensive cardiac work-up when clinical suspicion dictates. Further investigation is needed to understand the true prevalence of co-occurring multiprecursor amyloidosis affecting the heart and when cardiac tissue sampling should extend beyond the endomyocardium.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 4, 2024
AUGUST 2024:612–616

ACKNOWLEDGMENT The authors thank Jason Theis for his assistance in figure preparation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Karra has received institutional research support from Alnylam Pharmaceuticals and Intellia Therapeutics; and is a member of Alnylam Pharmaceuticals Speakers Bureau. Dr Costa Chase has received institutional research support from GlaxoSmithKline; and speaks on behalf of Sanofi. Dr Khouri has received institutional research support from Pfizer, BridgeBio Pharma, Alnylam Pharmaceuticals, and Ionis Pharmaceuticals; has received consulting/advisory board support from BridgeBio Pharma and Alnylam Pharmaceuticals; and is a member of Alnylam Pharmaceuticals Speakers Bureau. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Michel G. Khouri, Duke University School of Medicine, 40 Duke Medicine Circle, Room 3347, Orange Zone, Durham, North Carolina 27710, USA. E-mail: michel.khouri@duke.edu.

REFERENCES

1. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142(1):e7–e22. https://doi.org/10.1161/cir.0000000000000792

2. Mahmood S, Gilbertson JA, Rendell N, et al. Two types of amyloid in a single heart. *Blood*. 2014;124(19):3025–3027. https://doi.org/10.1182/blood-2014-06-580720

3. Sidiqi MH, McPhail ED, Theis JD, et al. Two types of amyloidosis presenting in a single patient: a case series. *Blood Cancer J*. 2019;9(3):30. https://doi.org/10.1038/s41408-019-0193-9

4. Donnelly JP, Gabrovsek A, Sul L, et al. Evidence of concurrent light chain and transthyretin cardiac amyloidosis in 2 patients. *J Am Coll Cardiol CardioOnc*. 2020;2(1):127–130. https://doi.org/10.1016/j.jaccao.2020.01.001

5. Moriyama H, Kitakata H, Endo J, et al. Step-by-step typing for the accurate diagnosis of concurrent light chain and transthyretin cardiac amyloidosis. *ESC Heart Fail*. 2022;9(2):1474–1477. https://doi.org/10.1002/ehf2.13773

6. Liepnieks JJ, Benson MD. Codeposition of transthyretin and immunoglobulin lambda light chain in senile cardiac (ATTR) amyloidosis. In: Grateau G, Kyle RA, Skinner M, eds. *Proceedings of Xth International Symposium on Amyloidosis*. CRC Press; 2004:332–333.

7. Shintani-Domoto Y, Ishino K, Naiki H, Sakatani T, Ohashi R. Autopsy case with concurrent transthyretin and immunoglobulin amyloidosis. *Pathol Int*. 2022;72(1):65–71. https://doi.org/10.1111/pin.13179

8. Connors LH, Prokaeva T, Lim A, et al. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. *Am Heart J*. 2009;158(4):607–614. https://doi.org/10.1016/j.ahj.2009.08.006

9. Kourelis TV, Dasari S, Theis JD, et al. Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry. *Blood*. 2017;129(3):299–306. https://doi.org/10.1182/blood-2016-10-743997

10. Dungu JN, Valencia O, Pinney JH, et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. *J Am Coll Cardiol Img*. 2014;7(2):133–142. https://doi.org/10.1016/j.jcmg.2013.08.015

KEY WORDS amyloid light chain, amyloidosis, cardiac biopsy, transthyretin