Journal of Community Hospital Internal Medicine Perspectives

Volume 12 | Issue 6 Article 15

2022

Concurrent Waldenstrom Macroglobulinemia and Mutant Transthyretin Cardiac Amyloidosis

Xiaoxiao Qian
Department of Cardiology, Inova Heart and Vascular Institute, Falls Church, Virginia, USA,
xiaoxiao.qian@inova.org

Hooman Bakhshi
Departemt of Cardiology, Inova Heart and Vascular Institute, Falls Church, Virginia, USA

Rakesh Biswas
Departemt of Hematology and Oncology, Inova Fairfax Hospital, Falls Church, Virginia,

Raghav Gattani
Departemt of Cardiology, Inova Heart and Vascular Institute, Falls Church, Virginia,

Jamie L Kennedy
Department of Advanced Heart Failure and Transplant, Inova Heart and Vascular Institute, Falls Church, Virginia,

CASE REPORT

Concurrent Waldenstrom Macroglobulinemia and Mutant Transthyretin Cardiac Amyloidosis

Xiaoxiao Qian [a,*], Hooman Bakhshi [a], Rakesh Biswas [b], Raghav Gattani [a], Jamie L. Kennedy [c]

[a] Departemt of Cardiology, Inova Heart and Vascular Institute, Falls Church, VA, USA
[b] Departemt of Hematology and Oncology, Inova Fairfax Hospital, Falls Church, VA, USA
[c] Department of Advanced Heart Failure and Transplant, Inova Heart and Vascular Institute, Falls Church, VA, USA

Abstract

Cardiac amyloidosis is caused by abnormal deposit of amyloid in the myocardium and can be divided into light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis. ATTR amyloidosis can be further divided into wild-type and mutant type based on genetic mutation. Differentiation between AL, wild-type, and mutant type ATTR amyloidosis has significant prognostic and therapeutic implications.

Keywords: Waldenstrom macroglobulinemia, Cardiac amyloidosis, Endomyocardial biopsy

1. Introduction

Waldenstrom macroglobulinemia (WM) is a rare disease characterized by lymphoplasmacytic lymphoma in the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy in the blood, it is uncommonly associated with AL amyloidosis and rarely with wild type ATTR amyloidosis. There has been no reported case of concurrent WM and mutant ATTR (mATTR) cardiac amyloidosis.

2. Case presentation

A 76-year-old African American male with medical history of chronic kidney disease stage 3 presented to urgent care with one month of dyspnea on exertion and orthopnea. Vitals signs were normal and physical exam was remarkable for rales in bilateral lungs and 1+ pitting edema of bilateral legs. Initial laboratory work was significant for troponin of 0.13 ng/ml (reference range ≤0.07 ng/ml) and B type natriuretic peptide (BNP) of 552 pg/ml (reference range ≤100 pg/ml). Electrocardiogram (ECG) indicated new atrial fibrillation and low voltage QRS (Fig. 1). Chest X-ray showed cardiomegaly and small bilateral pleural effusion. Patient was given furosemide 40 mg intravenously and observed in urgent care for 6 h. His shortness of breath improved with diuresis, and he was discharged home.

Patient was seen by cardiologist the next day. An echocardiography was obtained and showed significant left ventricular hypertrophy (LVH) (Fig. 2) and global hypokinesis with left ventricular ejection fraction of 35%. Exercise myocardial perfusion test did not show any reversible ischemia. The clinical suspicion for infiltrative cardiomyopathy was high given elevated BNP and troponin, low voltage QRS on ECG, new onset atrial fibrillation as well as LVH on echocardiogram. Serum and urine studies were obtained to evaluate for infiltrative cardiomyopathy. Serum electrophoresis showed M-spike migrating in the gamma globulin region. Urine electrophoresis was positive for free light chains with Kappa light chain of 148.41 mg/L (reference range ≤32.90 mg/L), Lambda light chain of 19.39 mg/L (reference range ≤3.79 mg/L), and a Kappa to Lamda ratio of 7.65 (abnormal ≥1.65). Serum and urine immunofixation demonstrated IgM Kappa monoclonal band. Abdominal fat pad biopsy was negative for amyloidosis. Bone marrow biopsy found low grade

Received 29 June 2022; revised 4 August 2022; accepted 18 August 2022.
Available online 7 November 2022

* Corresponding author. Department of Cardiology, Inova Heart and Vascular Institute, 3300 Gallows Rd, Falls Church, VA, 22042, USA.
E-mail address: xiaoxiao.qian@inova.org (X. Qian).

https://doi.org/10.55729/2000-9666.1117

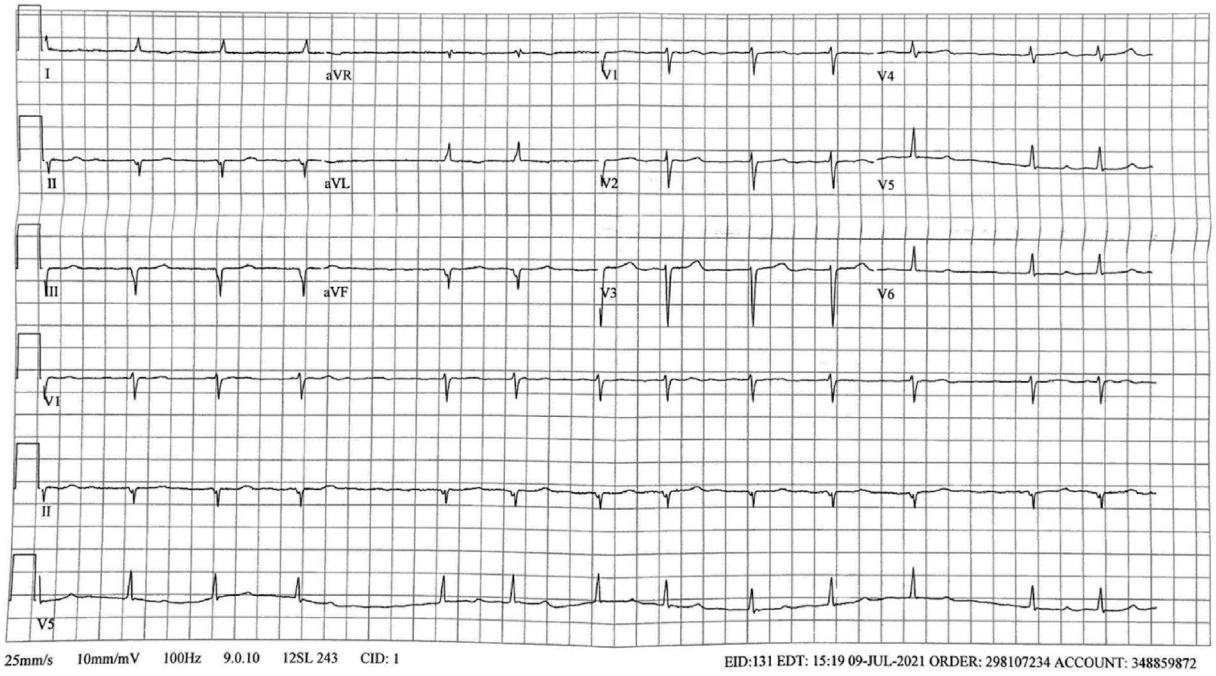

Fig. 1. Electrocardiogram showed atrial fibrillation, left axis deviation and low voltage QRS.

B-cell neoplasm, in the setting of IgM Kappa monoclonal gammopathy this was highly suspicious for WM. Genetic testing found MYD88 L265P gene mutation, which confirmed the diagnosis of WM.

A cardiac magnetic resonance imaging was obtained given continued suspicion of cardiac amyloidosis (CA) despite negative bone marrow and abdominal fat pad biopsy, and it demonstrated diffuse subendocardial enhancement with areas of mid-myocardial enhancement (Fig. 3), which was consistent with CA. Endomyocardial biopsy was proceeded. Hematoxylin and eosin staining of

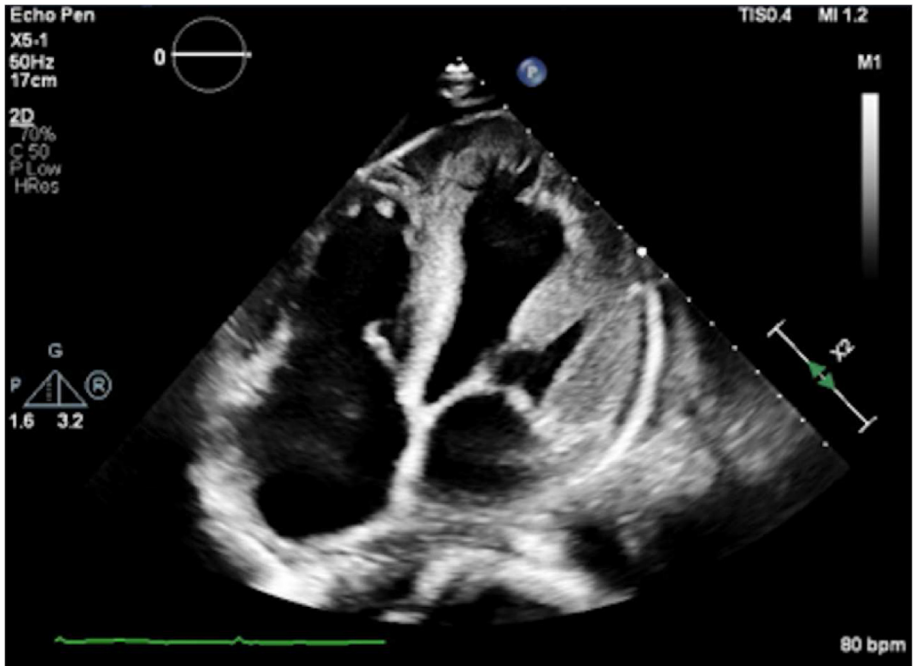

Fig. 2. Echocardiogram indicated significant left ventricular hypertrophy, mildly thickened mitral and tricuspid valve leaflets, and small pericardial effusion.

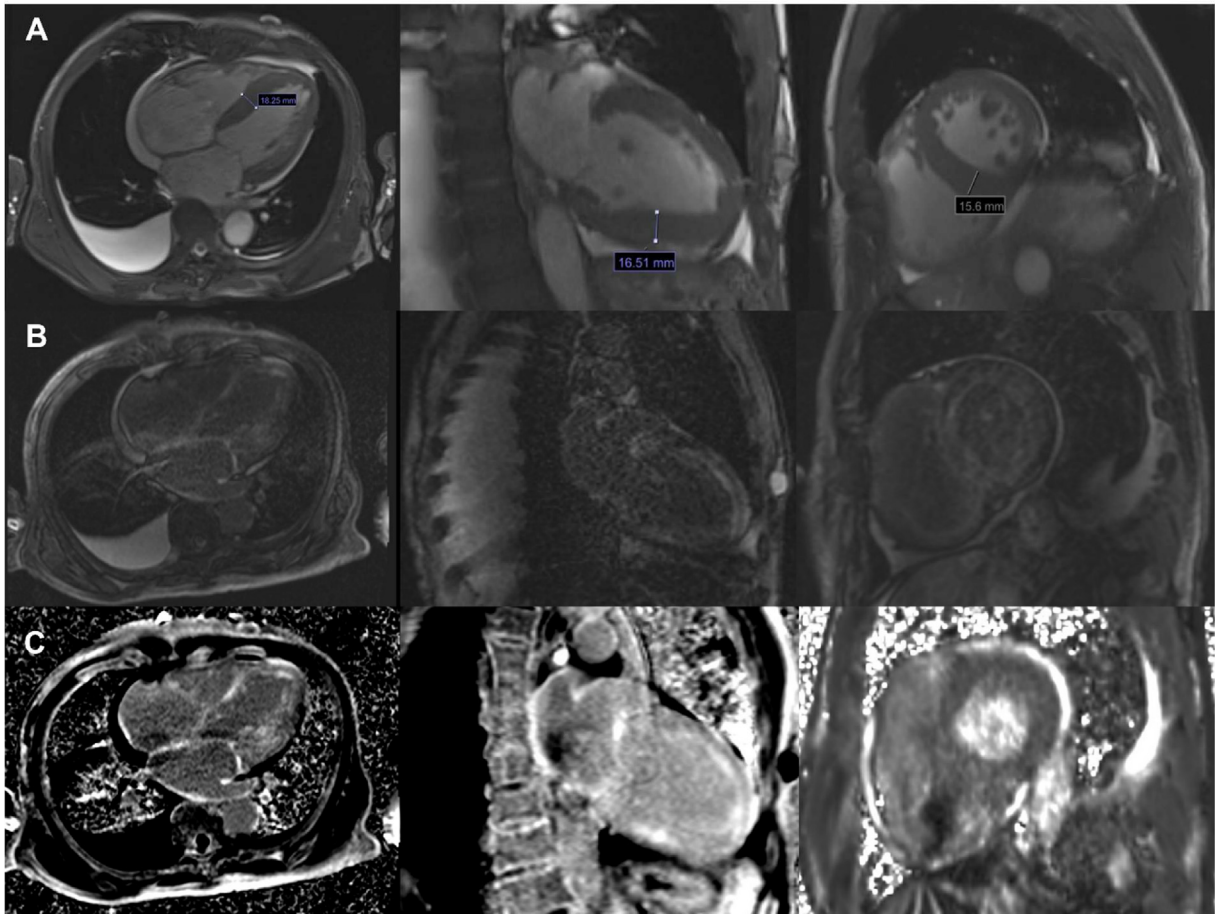

Fig. 3. Cardiac magnetic resonance demonstrated (A) Cine images with left ventricular hypertrophy; (B) Late gadolinium enhancement with diffuse gadolinium enhancement of myocardium; (C) Phase sensitive inversion recovery showed diffuse myocardial gadolinium enhancement.

endomyocardial biopsy samples showed Congo red-positive amyloid deposits (Fig. 4). Liquid chromatography–mass spectrometry (LC MS/MS) of peptides extracted from Congo red-positive specimen detected a peptide profile consistent with ATTR type amyloid deposition. LC MS/MS also detected an amino acid sequence abnormality Val142Ile in the TTR protein. Formal genetic testing confirmed Val142Ile pathogenic mutation.

Patient was started on tafamidis 61 mg daily for ATTR amyloidosis. His first-degree relatives were advised to have genetic testing. No treatment for

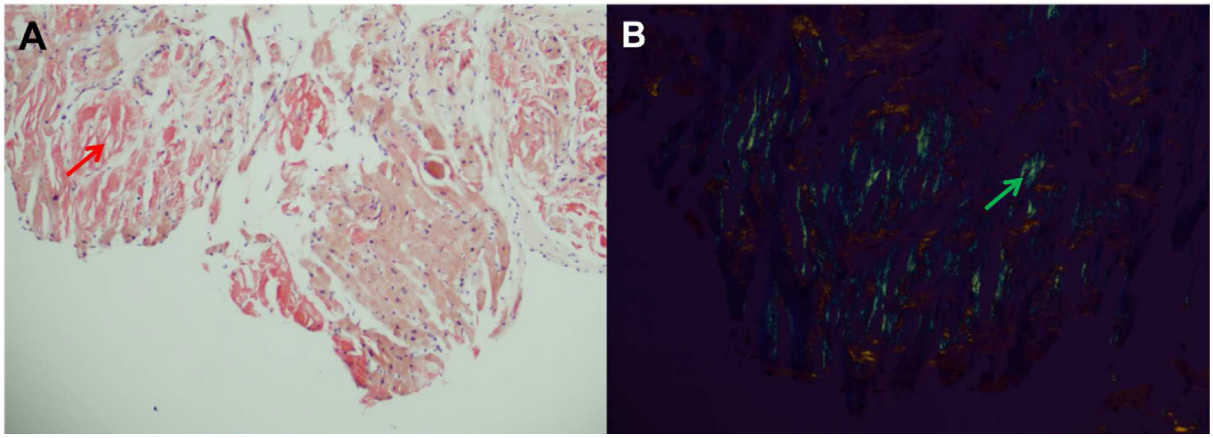

Fig. 4. Endomyocardial biopsy A. Congo red staining showed amyloid deposits (red arrow); B. Amyloids deposits in fluorescent green (green arrow).

WM was initiated and he was recommended to follow up with hematologist regularly.

3. Discussion

WM is a rare disorder with an incidence of 3.4 cases per million per year in males in the United States and 1.7 cases per million per year in females. Median age at presentation is about 70 years old. WM are predominantly found in Americans of European descent with African Americans representing only 5% of patients.[1] About a quarter of patients with WM have no symptoms or anemia attributable to IgM monoclonal protein infiltration. These patients are considered to have smoldering WM and do not need treatment. One of the indications for treatment is AL amyloidosis.

CA is caused by abnormal deposit of amyloid in the myocardium, and it can present with atrial fibrillation, heart failure as well as conduction disorders. The subtypes of CA include AL, wide type ATTR and mATTR amyloidosis. Val142Ile is the most common mutation seen in patients with mATTR amyloidosis. Among patients of African American descent, the reported prevalence of Val142IIe is 1.1−9.8% while in the general population this ranges from 0.3 to 1.6%. Typically, Val142IIe variant ATTR amyloidosis presents in the seventh to eighth decade of life.[2] With the advancement of noninvasive diagnostic methods, especially Technetium-99m Pyrophosphate scintigraphy (^{99m}Tc-PYP), ATTR amyloidosis can be diagnosed without endomyocardial biopsy.[3] However, a positive PYP scan in patients with plasma cell dyscrasia does not exclude AL amyloidosis, as in rare cases AL amyloidosis and ATTR amyloidosis can coexist.[4] The sensitivity of abdominal fat pad biopsy for detecting AL, mATTR and wild type ATTR amyloidosis was only estimated to be 84%, 45% and 15%, respectively.[5] In patients with suspected CA and abnormal free light chains on immunofixation, endomyocardial biopsy is the only method to make definitive conclusion.

AL amyloidosis complicates about 3% of WM cases based on previous studies.[6,7] Patients with AL amyloidosis and WM have higher tendency for amyloid-associated cardiomyopathy compared to other AL cases.[7] However, CA in patients with WM is not always AL amyloidosis, case series have demonstrated that WM can coexist with wild type ATTR amyloidosis,[8] especially as both diseases primarily affect the elderly population. Differentiation between AL and ATTR amyloidosis has significant prognostic and therapeutic implications. Patients with WM and AL CA have a shorter life expectancy compared to patients without CA and treatment focuses on the underlying hematological disease.[6] Treatment of ATTR amyloidosis, on the other hand, focuses on preventing further accumulation of the transthyretin protein, primarily with tafamidis, a small molecule which stabilizes transthyretin tetramers. The ATTR-ACT study showed mortality and morbidity benefit of tafamidis in treatment of ATTR cardiomyopathy and the recently published long-term outcome data again confirmed the significant survival benefit.[9,10]

Patient has been doing well from cardiac as well as hematological standpoints 12 months after diagnosis.

4. Conclusion

To our best knowledge, to this date there has been no case reported with concurrent WM and mATTR amyloidosis. This case highlights the importance to keep all types of cardiac amyloidosis in differential diagnoses and to perform endomyocardial biopsy in patients with plasma cell dyscrasia to confirm the diagnosis.

Notes on patient consent

Written consent for publication was obtained from patient.

Disclaimer

All authors disclaim that the article has not been submitted to other publications; an abstract of this case was presented at a conference (American College of Cardiology 22, Washington, DC, April 2nd-4th, 2022).

Source of support

This case report has no funding. The publication fee will be paid by our fellowship program if accepted.

Conflict of interest

All authors have no conflict of interest to report.

References

1. Fonseca R, Hayman S. Waldenström macroglobulinaemia. *Br J Haematol*. 2007:700−720.
2. Chandrashekar P, Alhuneafat L, Mannello M, et al. Prevalence and outcomes of p.Val142Ile TTR Amyloidosis cardiomyopathy: a systematic Review. *Circ Genom Precis Med*. 2021; 14(5), e003356.
3. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American heart association. *Circulation*. 2020;E7−22.

4. Sidiqi MH, McPhail ED, Theis JD, et al. Two types of amyloidosis presenting in a single patient: a case series. *Blood Cancer J [Internet]*. 2019;9(3).
5. Quarta CC, Gonzalez-Lopez E, Gilvertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J*. 2017 Jun 21;38(24):1905—1908.
6. Gertz MA, Kyle RA, Noel P. Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenström's macroglobulinemia. *J Clin Oncol*. 1993;11(5).
7. Terrier B, Jaccard A, Harousseau JL, et al. The clinical spectrum of IgM-related amyloidosis: a French nationwide retrospective study of 72 patients. *Medicine (Baltim)*. 2008;87(2): 99—109.
8. Singh A, Geller HI, Alexander KM, et al. True, true unrelated? Coexistence of waldenström macroglobulinemia and cardiac transthyretin amyloidosis. *Haematologica*. 2018;103(8): e374—e376.
9. Mauer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007—1016.
10. Elliott P, Drachman BM, Gottlied SS, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail*. 2022 Jan;15(1), e008193.