

# Mitral and tricuspid stenosis caused by light chain cardiac amyloid deposition

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## Abstract

Cardiac amyloidosis results in an infiltrative restrictive cardiomyopathy, with a number of characteristic features: biventricular hypertrophy, abnormal myocardial global longitudinal strain with relative apical sparing, biatrial dilation, and small pericardial effusion along with conduction abnormalities. Amyloid deposits leading to hemodynamically significant valvular heart disease are very rare. We describe a rare case of concomitant moderately severe tricuspid and mitral valve stenosis because of ongoing amyloid deposition in a patient with progressive multiple myeloma and fat pad biopsy-proven light chain amyloidosis. Worsening infiltrative cardiomyopathy and valvulopathy despite evidence-based chemotherapy and heart failure pharmacotherapy led to end-stage disease and death. Valvular involvement in cardiac amyloidosis requires early recognition of the underlying disease condition to guide directed medical therapy and prevent its progression. In this instance, valvuloplasty or valve replacement is not a viable option.

**Keywords** Light chain amyloid valvulopathy; Light chain cardiac amyloidosis; Mitral stenosis; Tricuspid stenosis

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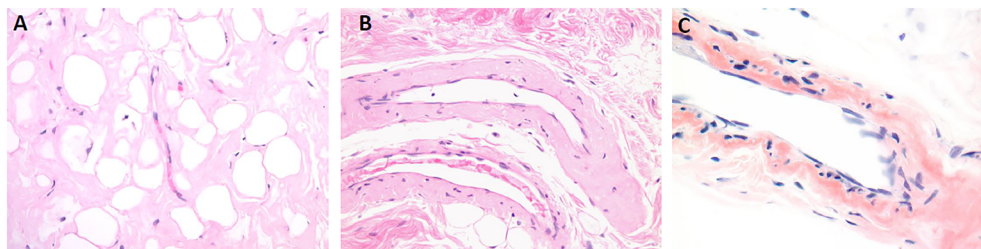
## Introduction

The two main types of amyloidosis that affect the heart are light chain (AL) and transthyretin.<sup>1,2</sup> Multiple myeloma and AL amyloidosis can occur together in ~5–10% of patients (predominantly male patients and median age is 63 years).<sup>2</sup> In cardiac amyloidosis (CA), the aggregation and deposition of misfolded protease-resistant amyloid fibrils in the extracellular space cause an infiltrative cardiomyopathy associated with restrictive pathophysiology and characteristic echocardiographic features including biatrial enlargement, diffuse biventricular thickening, pericardial effusion, and mild to moderate thickening of the valve leaflets.<sup>1,2</sup> There are limited case reports of amyloid deposits causing moderate to severe valvular heart disease.<sup>3–7</sup> Herein, we describe a rare instance of hemodynamically significant tricuspid and mitral valve stenosis because of cardiac AL amyloidosis.

## Case report

A 57-year-old African American male patient was first diagnosed in 2015 with multiple myeloma (60% clonal plasma cells on bone marrow biopsy) and AL amyloidosis (confirmed by fat pad biopsy; *Figure 1*). He presented with signs and symptoms of New York Heart Association class III heart failure (elevated jugular venous pulse at 12-cm H<sub>2</sub>O and 2+ peripheral and scrotal oedema), macroglossia, and bilateral carpal tunnel syndrome. His past medical history included atrial fibrillation and stage 3 chronic kidney disease. Cyclophosphamide, bortezomib (switched to lenalidomide because of peripheral neuropathy), and dexamethasone were initiated at diagnosis as first-line therapy. Intravenous chemotherapy was replaced by an oral regimen to enhance medication compliance in 2016, which improved light chain response. In late 2018, this regimen was replaced by the

**Figure 1** Light microscopy of fat pad biopsy. (A and B) Haematoxylin and eosin-stained sections show dense amorphous eosinophilic material, characteristic of amyloid, between adipocytes and in the vessel wall, respectively (200× magnification). (C) Congo red staining shows typical dense ‘orangeophilic’ staining of amyloid in the vessel wall (400× magnification).

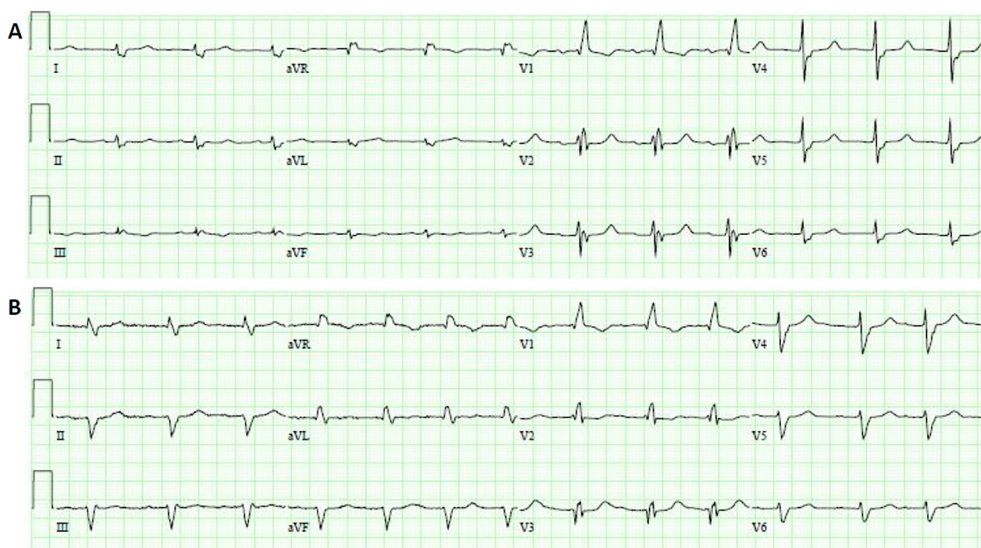


**Table 1** Fluctuating serum biomarkers coincident with progression of light chain amyloidosis

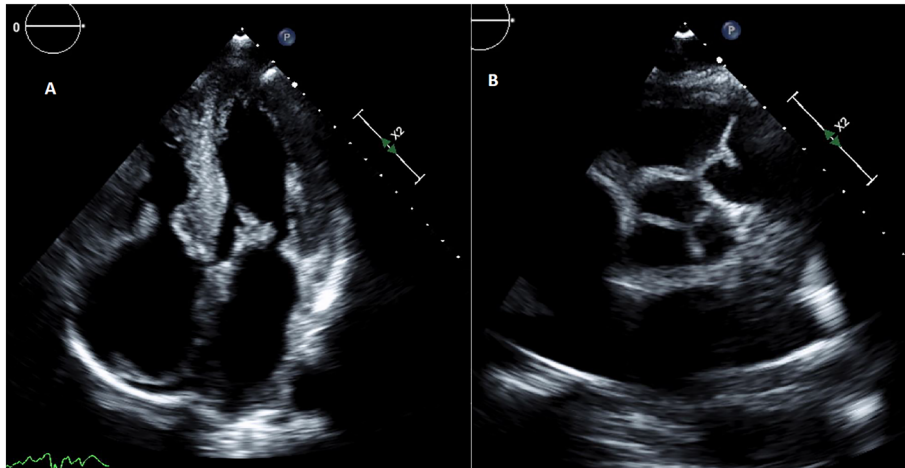
Parameter	At diagnosis mid-2015	2016	2017	2018	2019
Serum creatinine (mg/dL)	1.13	0.99	0.98	1.47	1.38
eGFR	>60	>60	>60	59	53
Troponin T (ng/mL)	0.023	0.018	<0.010	0.019	0.013
NT-proBNP (pg/mL)	2265	1748	974	1093	2107
Leukocytes (k/ $\mu$ L)	3.62	2.36	4.08	5.36	6.75
M protein	Present	Present	Present	Present	Present
Serum IgG (mg/dL)	1440	1360	1430	1630	1150
Serum IgA (mg/dL)	87	119	234	254	122
Serum IgM (mg/dL)	39	51	61	100	51
Serum free kappa (mg/L)	4488	1331.2	628.4	899.4	949
Serum free lambda (mg/L)	8.8	11.1	9.4	9.7	9.1
K/L ratio	510	119.9	66.9	92.7	104.3
Other relevant tests	CRP 0.1 mg/dL	—	—	—	Urine K/L ratio 4478.3; procalcitonin 18.3 ng/mL
Therapy initiated	Triple therapy: cyclophosphamide, bortezomib (stopped for peripheral neuropathy), dexamethasone; lenalidomide (added)	Switched to oral from intravenous regimen (because of patient non-adherence)	—	Switched to Daratumumab (given as monotherapy for disease progression because of patient non-compliance)	-

eGFR, estimated glomerular filtration rate; NT-proBNP, N terminal pro BNP.

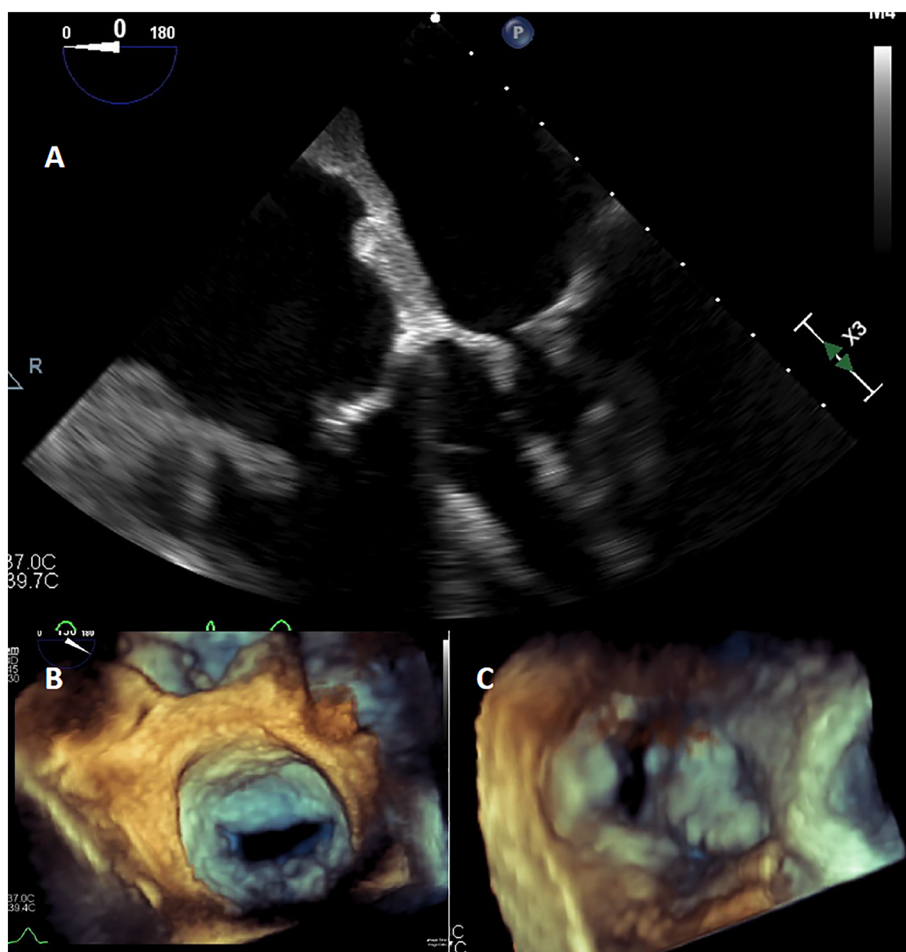
**Figure 2** Electrocardiograms demonstrating evolving conduction disease: (A) Baseline sinus rhythm with first degree atrio-ventricular block. (B) Atrial fibrillation with left axis deviation, left fascicular block, complete right bundle branch block, and anterior lead pseudo-infarct pattern.



**Figure 3** Transthoracic echocardiogram: (A) Apical four-chamber view demonstrating thickened mitral and tricuspid valve leaflets with evidence of restricted opening and stenosis and a trace effusion around the right atrium. (B) Parasternal short axis view of the aortic and pulmonic valves demonstrating diffuse thickening.



**Figure 4** Transoesophageal echocardiogram: (A) Mid-oesophageal four-chamber view demonstrating diffuse thickening of the mitral and tricuspid valves with restricted opening and stenosis. (B) Three-dimensional surgeons view of the stenotic mitral valve. (C) Three-dimensional view from the right atrium of the stenotic tricuspid valve.



CD38 monoclonal antibody daratumumab in response to rising serum light chains, progressive CA, and recurrent admissions for decompensated heart failure (elevated jugular venous pulse at 15 cm, 3+ peripheral and scrotal oedema, and dyspnoea at rest) in the setting of ongoing patient non-adherence.

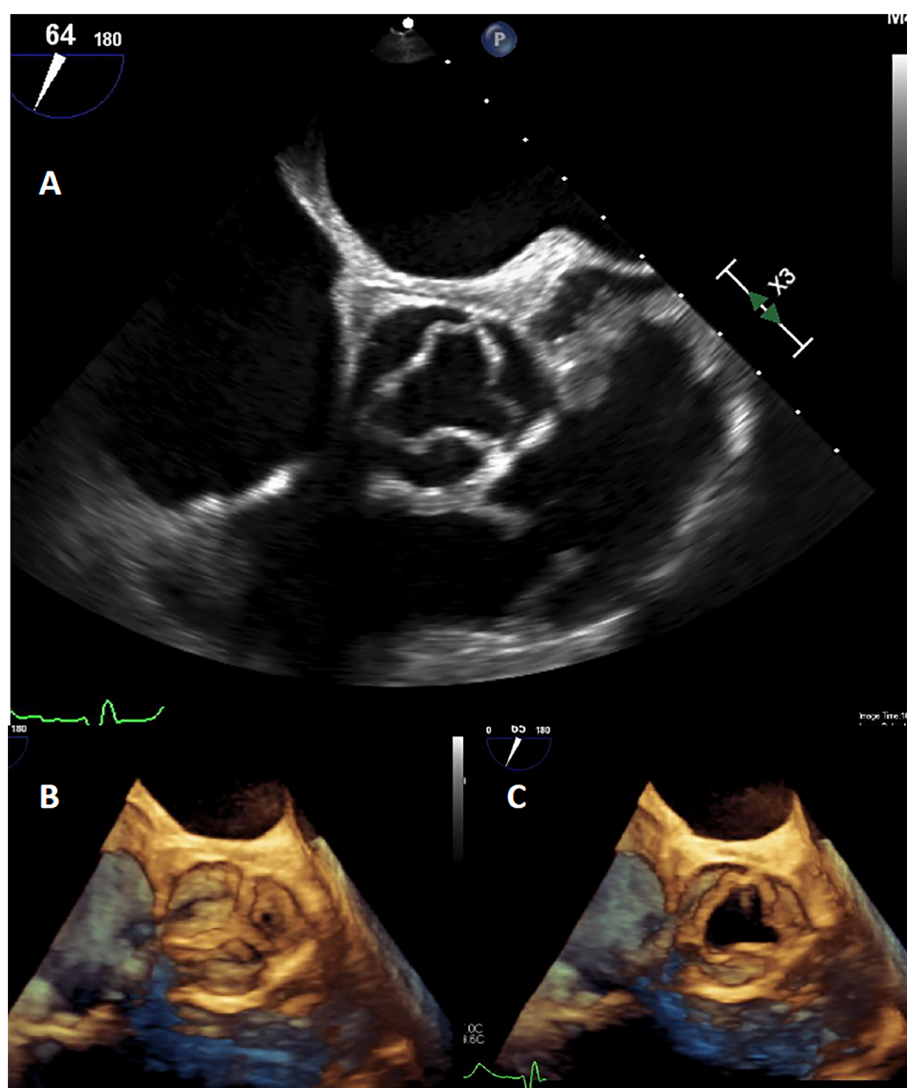
Over time, serial N terminal pro BNP, troponin T, and serum creatinine levels fluctuated along with serum M proteins and light chains, coincident with progression of AL amyloidosis (Table 1). Electrocardiograms revealed evolving conduction disease (Figure 2).

Transthoracic echocardiogram demonstrated features consistent with CA: normal left ventricular size, preserved ejection fraction, biatrial dilation with atrial thickening,

biventricular hypertrophy (1.2–1.6 cm), trivial pericardial effusion, and abnormal myocardial global longitudinal strain (−13.9%) with relative sparing of the apex and a relative regional strain ratio of 2.1 (Figure 3).

Interestingly, transthoracic echocardiogram also had evidence of progressive valvular disease with stenosis of the tricuspid and mitral valves coincident with worsening AL amyloidosis (Figure 3; Table 1). This stenosis was further interrogated with transoesophageal echocardiogram (Figures 4 and 5 and Figure S1). Transoesophageal echocardiogram demonstrated diffuse thickening of the tricuspid valve leaflets and sub-valvular apparatus causing restricted leaflet motion and moderately severe tricuspid stenosis (mean gradient 4 mm Hg and peak gradient 8 mm Hg)

**Figure 5** Transoesophageal echocardiogram: (A) Mid-oesophageal aortic valve short axis demonstrating diffuse thickening of the aortic, tricuspid, and pulmonic valves and of the intra-atrial septum and atrial wall. (B) Three-dimensional image of the thickened aortic valve leaflets in diastole. (C) Three-dimensional image of the thickened aortic valve leaflets in systole.



and moderate tricuspid regurgitation. Similarly, there was thickening of the mitral valve leaflets leading to restricted leaflet motion and moderately severe mitral stenosis (mean gradient 9 mm Hg and peak gradient 24 mm Hg at 67 bpm; mitral valve area 1.5 cm<sup>2</sup> by 3-D-planimetry) with mild mitral regurgitation. The aortic and pulmonic valves also demonstrated prominent and diffuse thickening, albeit without haemodynamically significant valvular stenosis or regurgitation.

## Discussion

CA carries significant morbidity and poor survival prognosis without therapy.<sup>1,2</sup> AL amyloidosis results from the accumulation of misfolded immunoglobulin light chains formed by an abnormal clone of plasma B cells and can be associated with multiple myeloma.<sup>2</sup> In AL amyloidosis, cardiac involvement drives prognosis, and prompt recognition and treatment are vital to prevent worsening heart failure.<sup>1,2</sup> Our patient experienced progressive multi-valvular heart disease concomitant with CA progression (*Table 1; Figures 3–5*) with valve leaflets becoming moderately thickened, resulting in moderately severe tricuspid and mitral stenosis, with moderate tricuspid and mild mitral regurgitation because of accompanying restricted leaflet motion.

There are case reports of amyloid deposition restricted to valvular tissue because of dystrophic valvular amyloidosis.<sup>6</sup> Here, the amyloid deposits are commonly associated with localized calcified deposits and scar tissue resulting from chronic inflammation or mechanical trauma.<sup>6</sup> In a recent study of surgically excised heart valves, the prevalence of amyloid deposits was found to be highest in aortic stenosis (74%), relative to mitral stenosis or regurgitation (~29%) and aortic regurgitation (10.5%).<sup>4</sup> Abnormal left heart valve thickening, notable in 42% of patients with confirmed AL amyloidosis, correlated with higher all-cause mortality (hazard ratio 1.9 and  $P = 0.02$ ), more advanced disease, worse New York Heart Association functional class, and lower 5-year survival in these patients.<sup>7</sup> The incidence of tricuspid stenosis and regurgitation has not been well described and is very rare. While tricuspid and mitral stenosis can be seen in rheumatic heart disease, our patient did not report a past history of rheumatic fever and does not have valve calcification on imaging.<sup>8</sup> This case highlights the rare incidence of haemodynamically significant valvulopathy that can be associated with refractory CA.

The role of valvuloplasty in valvular heart disease because of CA remains unexplored. We hypothesize that valvuloplasty

may not be effective in this case because valve commissures are open and the primary defect is leaflet thickening. Surgical valve replacement would be high risk because of poor outcomes with cardiac surgery in patients with restrictive cardiomyopathy.

## Conclusions

This report highlights a rare case of hemodynamically significant tricuspid and mitral stenosis caused by progressive leaflet thickening in the setting of light chain CA despite prior pharmacotherapy. Worsening clinical heart failure occurred as circulating light chains increased and valvular thickening and stenosis progressed. The role of routine valvular interventions in CA is not well defined and may be high risk because of concomitant restrictive cardiomyopathy.

## Conflict of interest

Dr. Perez is an advisory board member/consultant for Abiomed.

## Funding

None.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Videos of transesophageal echocardiograms: A) Mid esophageal four chamber view demonstrating diffuse thickening of the mitral and tricuspid valves with restricted opening and stenosis. B) 3D surgeons view of the stenotic mitral valve. C) 3D view from the right atrium of the stenotic tricuspid valve. D) Mid esophageal aortic valve short axis demonstrating diffuse thickening of the aortic, tricuspid, and pulmonic valves; and of the intra-atrial septum and atrial wall. E) 3D view of the thickened aortic valve.

**Data S2.** Supporting Information

**Data S3.** Supporting Information

**Data S4.** Supporting Information

**Data S5.** Supporting Information.

## References

1. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med* 2017; **84**: 12–26.
2. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J Am Coll Cardiol* 2016; **68**: 1323–1341.
3. Kim KH, Park CH, Park HS, Kim YR, and Choi EY. Amyloidosis-induced tricuspid mimicking rheumatic heart disease. *Eur Heart J Cardiovasc Imaging* October 2014; **15** (10): 1167.
4. Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, Koch A, Sack FU, Katus HA, Linke RP, Dengler TJ. High prevalence of amyloid in 150 surgically removed heart valves—a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions. *Cardiovasc Pathol* 2010; **19**: 228–235.
5. Krishnaswamy A, Hanna M, Goodman A, Kapadia SR. First reported case of MitraClip placement due to mitral valve flail in the setting of cardiac amyloidosis. *Circ Heart Fail*. 2016 Aug; **9**(8): pii: e003069.
6. Cooper JH. Localized dystrophic amyloidosis of heart valves. *Hum Pathol* Jul 1983; **14**: 649–653.
7. Mohty D, Pradel S, Magne J, Fadel B, Boulogne C, Petitalot V, Raboukhi S, Darodes N, Damy T, Aboyans V, Jaccard A. Prevalence and prognostic impact of left-sided valve thickening in systemic light-chain amyloidosis. *Clin Res Cardiol* 2017; **106**: 331–340.
8. Mirabel M, Celermajer DS, Ferreira B, Tafflet M, Perier MC, Karam N, Mocumbi AO, Jani DN, Sidi D, Jouven X, Marijon E. Screening for rheumatic heart disease: evaluation of a simplified echocardiography-based approach. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 1024–1029.