

Rapid progression of aortic and mitral stenosis in a patient with AA amyloidosis: a case report

David Frumkin ^{1*}, Eliane Tabea Taube², Karl Stangl¹, and Fabian Knebel¹

¹Department of Cardiology and Angiology, Campus Mitte, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; and ²Department of Pathology, Campus Mitte, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

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Background

Aortic stenosis is a common finding in cardiac amyloidosis (CA). Younger patients often remain asymptomatic. If unrecognized, this can lead to serious complications such as heart failure. Progression of aortic stenosis can be accelerated in patients with chronic kidney disease and need for dialysis. Perioperative risk in these patients is often high due to the underlying systemic disease.

Case summary

A 40-year-old Caucasian man with known AA amyloidosis, highly active Ankylosing Spondylitis and need for chronic dialysis due to end-stage chronic renal failure presented for echocardiographic routine exam without reporting any cardiac symptoms. At the last visit 4 years ago, a normal heart valve function was noted and no echocardiographic follow-up was performed in the following. Now, rapid progression with severe aortic valve and mitral valve stenosis was stated and the patient underwent combined aortic and mitral surgical valve replacement following discussion in the multidisciplinary cardiology meeting. Macroscopic examination of the valves revealed significant calcification and histological examination showed the high presence of amyloid by Congo-red staining and immunohistological staining for AA-Amyloid. Both valve prosthetic devices showed normal function as well as a normal left ventricular ejection fraction in initial post-operative transoesophageal echocardiography. After prolonged and complicated post-operative course in the intensive care unit the patient died 3 months after surgery due to intractable multiorgan failure in combined severe abdominal septic and cardiogenic shock.

Discussion

Concomitant CA and chronic dialysis can accelerate the onset of severe aortic valve stenosis. Young patients, as in this case, often stay asymptomatic, perioperative risk increases with duration of chronic dialysis and severity of valve stenosis. This increases the need for regular short-term echocardiographic examinations even in clinical stable patients.

Keywords

Cardiac amyloidosis • Left ventricular hypertrophy • Aortic valve stenosis • Mitral valve stenosis • Chronic kidney disease • Dialysis • Case report

Learning points

- Concomitant cardiac amyloidosis and dialysis can accelerate the onset of severe aortic valve stenosis.
- Regular frequent echocardiographic follow-up, even in clinically stable patients, is important.

* Corresponding author. Tel: 0049/ 30-450-613194, Fax: +49 30 450 7513 932, Email: david.frumkin@charite.de

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Introduction

Cardiac amyloidosis (CA) is a rare cause of myocardial thickening predominantly caused by abnormal deposition of myocardial light chain or transthyretin amyloid.¹ A scarcer cause of CA is systemic AA amyloidosis, in which the deposited protein is serum amyloid A protein, an acute-phase protein which is normally soluble and whose plasma concentration is highest during inflammation. The most frequent underlying disorder is inflammatory arthritis. The predominant disease manifestation of AA amyloidosis at diagnosis is renal dysfunction.²

Diagnosis of cardiac involvement in systemic amyloidosis can be challenging. Echocardiographic signs of cardiac involvement are left ventricular wall thickening (left ventricular hypertrophy, LVH), preserved apical longitudinal contraction and basal hypokinesia ('apical sparing'), and an elevated apical-to-basal gradient ('cherry on the cake') of longitudinal strain.^{3–5} Additional diagnostic modalities such as late gadolinium magnetic resonance imaging or transcatheter cardiac biopsy are recommended by the current guidelines⁶ if uncertainties on the underlying diagnosis following echocardiography remain.

Aortic stenosis (AS) and other valve disorders secondary to amyloid deposition are common findings in systemic amyloidosis as well as in chronic dialysis patients, often requiring valve surgery.^{7,8} Recently, Galat et al.⁹ published a clinical description of 16 patients with concomitant aortic stenosis and CA, however, this relates to mainly older patients with transthyretin CA.

Since patients with systemic amyloidosis often have a high perioperative risk due to multiorgan involvement of the underlying disease, prognosis after valve surgery in these patients is poor.

We report a case of a 40-year-old Caucasian man with rapid progression of aortic and mitral valve stenosis secondary to AA amyloidosis and multiple complications after cardiac surgery.

Timeline

2014	First echocardiographic signs of cardiac involvement with left ventricular hypertrophy and typical apical sparing. No valve dysfunction, preserved left ventricular ejection fraction (LVEF). No cardiac symptoms
May 2018	Severe aortic valve stenosis and severe mitral valve stenosis, preserved LVEF. No cardiac symptoms
June 2018	Surgical aortic and mitral valve replacement
September 2018	Patient deceased due to post-operative complications with multiorgan failure

Case presentation

A 40-year-old Caucasian man presented to our cardiologic outpatient department for regular cardiac evaluation. Dyspnoea or other cardiologic symptoms were negated by the patient. AA amyloidosis and associated end-stage chronic renal failure with need for constant

dialysis due to highly active Ankylosing spondylitis was diagnosed 7 years ago and confirmed on kidney biopsy. At initial echocardiographic examination 4 years ago typical left ventricular wall thickening (19 mm) and 'apical sparing' with abnormal longitudinal function was stated, suspicion of CA was raised. Left ventricular ejection fraction (LVEF) was normal (60%). Yet, no aortic or mitral dysfunction was stated. No additional cardiac diagnostic modalities were done because of potential contrast agent side effects in absence of expected further therapeutic consequences. The patient continued his regular visits at the nephrology department. Due to arterial hypertension and LVH, regular antihypertensive and heart insufficiency medication was initiated (ramipril 5 mg b.i.d.; lercanidipine 10 mg b.i.d.). Anti-inflammatory therapy for ankylosing spondylitis consisted of 15 mg Prednisolone daily. Despite our recommendations no echocardiographic follow-up was performed in the following 4 years till the present visit.

In the present echo exam, the patient showed no change in LVH or LVEF. Surprisingly, while any cardiac symptoms were negated, the patient now showed severe aortic valve stenosis and mitral valve stenosis, the valves showing signs of massive calcification (see *Figures 1–4, Supplementary material online, Video S1*) (left ventricular end-diastolic volume: 51 mm, left ventricular end-systolic volume: 36 mm, no pericardial/pleural effusion, no left ventricular outflow tract obstruction, no systolic anterior movement, aortic valve mean pressure gradient: 30.56 mmHg, aortic valve Vmax: 3.8 m/s, aortic valve area: 1.1 cm², mitral valve mean pressure gradient: 13.92 mmHg, mitral valve area: 1.7 cm², no relevant aortic, mitral, or tricuspid valve regurgitation). N-terminal prohormone of brain natriuretic peptide was >70 000 ng/dL. Electrocardiogram showed regular sinus rhythm, without any conduction abnormalities. Clinical examination of the patient showed normal blood pressure (128/68 mmHg), normal heart rate (58 b.p.m.), rhythmic pulse and normal SpO₂ (98%) by pulse oximetry. Auscultation revealed a 3/6 systolic, crescendo-decrescendo murmur, heard loudest at the 2nd right intercostal space. No peripheral oedema or increased jugular vein pulse was present. No hepatic or splenomegaly was present. Physical examination showed overheated and swollen knee joints. Due to suspicion of progressive systemic amyloidosis and ankylosing spondylitis a therapy with interleukin-6-receptor monoclonal human antibody (Tocilizumab) was initiated.

Following discussion in the multidisciplinary cardiology meeting, the decision for surgical valve replacement of the aortic and mitral valve, due to fast progression, was made. A coronary angiography for preoperative evaluation showed no relevant coronary stenosis. Despite the high surgical risk in this patient, transcatheter aortic valve implantation was rejected by the Heart Team due to the young age and accompanying severe surgically treatable mitral valve disease in compliance with the current European Society of Cardiology (ESC) guidelines for the management of valvular heart disease.⁶

Surgical replacement of the aortic and mitral valve was conducted 8 weeks after severe aortic valve stenosis and mitral valve stenosis was diagnosed [23 mm Trifecta GT Aortic Valve (St. Jude Medical Abbott, St. Paul, MN, USA)/mitral valve prosthesis: 29 mm Hancock II (Medtronic, Dublin, Ireland)]. Macroscopic examination of the valves revealed significant calcification and were sent to our pathologic department for further examination. Both valve prosthetic devices

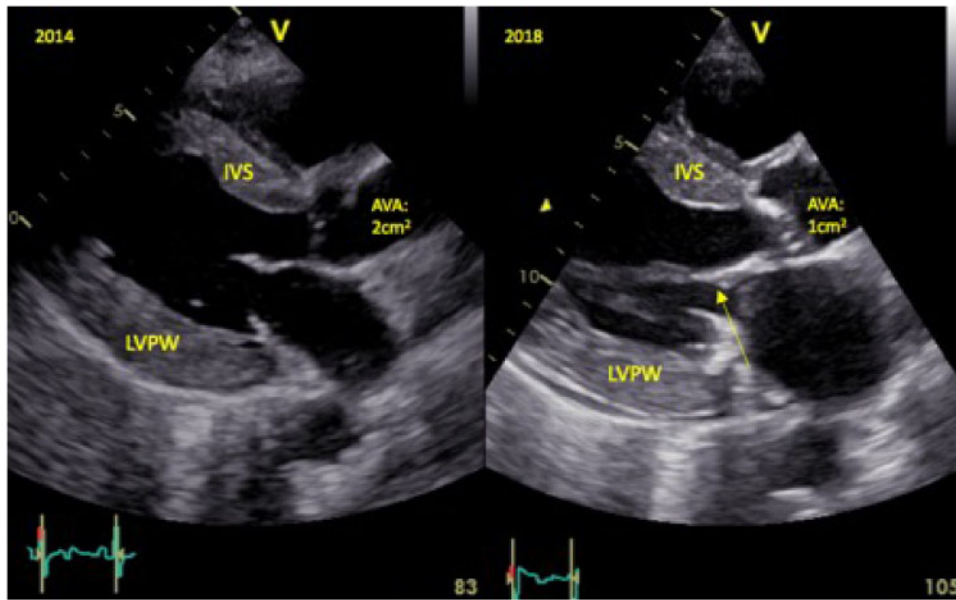


Figure 1 Comparison of the transthoracic parasternal long-axis view in end-diastole from 2014 (left) and 2018 (right). Both exams show left ventricular hypertrophy of interventricular septum = 19 mm (in 2014) and interventricular septum = 18 mm (in 2018). Aortic and mitral valve morphology is normal in 2014 and shows massive thickening and reduced mobility in 2018. Notice the thickened mitral valve leaflets indicated by the arrow. See also the additional [Supplementary material online, Video S1](#). AVA, aortic valve area; IVS, interventricular septum; LVPW, left ventricular posterior wall.

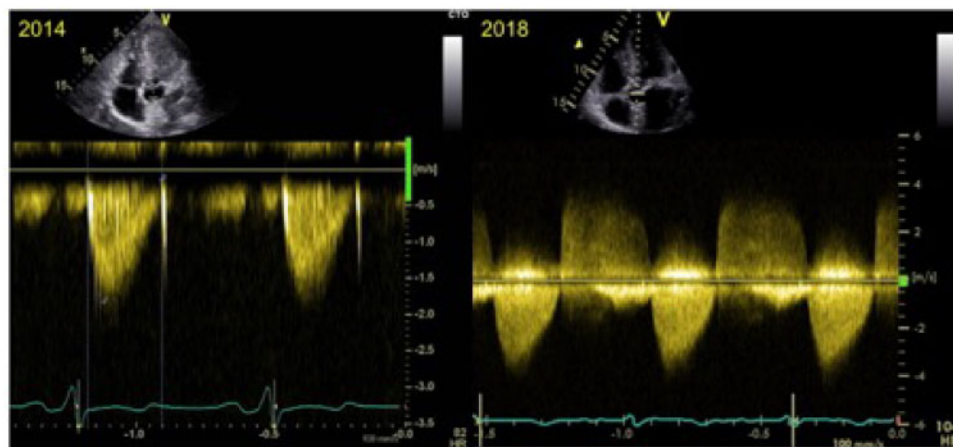


Figure 2 Comparison of apical five-chamber view with continuous wave Doppler across the aortic valve from 2014 (left) and 2018 (right, mean pressure gradient: 30.56 mmHg). 2018 shows elevated peak systolic velocities.

showed normal function as well as a normal LVEF in initial post-operative transoesophageal echocardiography.

Histopathological examination of the removed aortic and mitral valve showed severe calcification and the high presence of amyloid by Congo-red staining and immunohistological staining for AA-Amyloid (see [Figure 5](#)).

Post-operatively the patient suffered from severe systemic inflammatory response syndrome (SIRS) with prolonged weaning, recurrent respiratory and abdominal septic shocks, cardiogenic shock due to cardiac arrhythmias and multiple further complications. Respiratory weaning was complicated by recurrent hospital-acquired pneumonia with proof of *Citrobacter koseri* and *Stenotrophomonas*

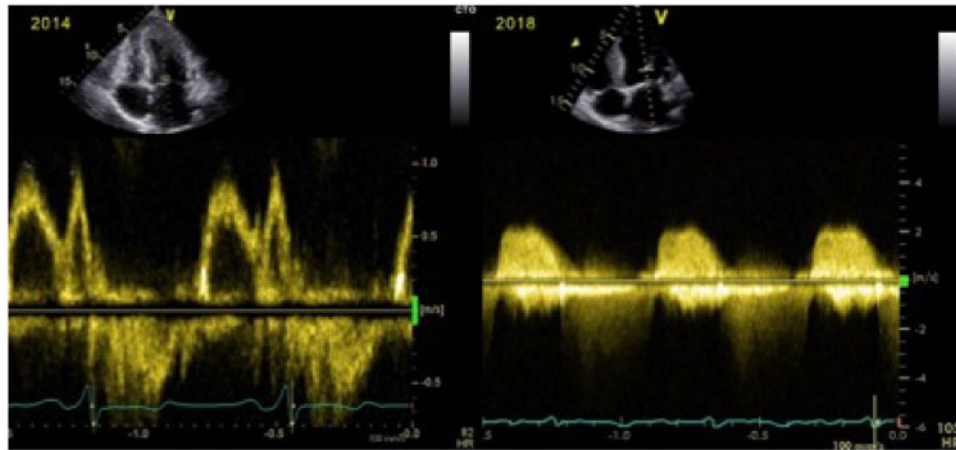


Figure 3 Comparison of apical four-chamber view with pulsed wave Doppler in 2014 and continuous wave Doppler in 2018 across the mitral valve. Notice the normal E/A ratio in 2014 and the typical mitral valve stenosis pattern in 2018 (mitral valve mean pressure gradient = 13.92 mmHg).

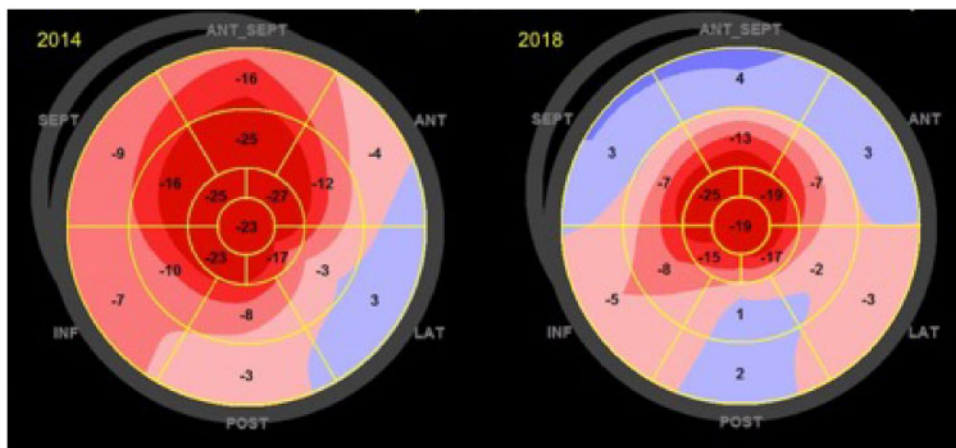


Figure 4 Comparison of left ventricular global longitudinal strain visualized with automated function imaging showing the typical apical sparing with the 'cherry on the cake' pattern already visible in 2014 (left) and intensified in 2018 (right). Outer circles correspond to the basal segments, the centre corresponds to the apical segment. The longitudinal strain is visualized with red colouring for high longitudinal strain and blue colouring for low longitudinal strain. Also, the longitudinal peak systolic strain apical to basal gradient [sum of apical strain values/(sum of mid + basal left ventricular strain values)] is clearly pronounced in 2018.

*malto*philia in bronchoalveolar lavage. Weaning remained without progress despite surgical tracheotomy and anti-infective treatment (Tazobactam/Piperacillin/Ciprofloxacin). Furthermore, the patient suffered from refractory *Clostridium difficile* enteritis, treated with vancomycin/ fidaxomicin. A rectoscopy in suspicion of gastrointestinal bleeding (decrease in haemoglobin, peranal haemorrhage) revealed a defect of distal rectum with tissue necrosis. Aetiology of the defect remained unclear. An endosponge was inserted by laparoscopy and a protective ileostomy was placed, local peritonitis was seen intraoperatively. Two days after bowel surgery, the patient's condition worsened with increasing demand of catecholamines in suspicion of abdominal septic shock. Additionally, the patient showed repeated

ventricular arrhythmias with necessity of 10 min of reanimation and multiple defibrillations. The patient died 3 months after surgical valve replacement due to intractable multiorgan failure.

Discussion

We present a case with rapid progression of cardiac involvement in systemic AA amyloidosis. Early diagnosis of CA was made at the stage of already wide systemic involvement, including terminal chronic kidney disease with necessity for dialysis and signs of cardiac remodelling, but at that time no involvement of the valves or signs of cardiac



Figure 5 Histology of the aortic valve biopsy specimen revealed amyloid deposits. Arrows indicate the amyloid positive area. Left: Congo red staining ($\times 100$). Right: anti-amyloid A immunohistochemistry of the same area ($\times 100$).

decompensation. The patient developed severe aortic stenosis and mitral valve stenosis in the period of 4 years, without presence of cardiac symptoms. It must be considered that in this patient with reduced mobility due to the underlying rheumatic disease and chronic dialysis, awareness of cardiac symptoms such as dyspnoea and reduced exercise capacity was low.

The mechanisms of aortic stenosis in AA amyloidosis are yet not fully understood. On the one hand, in the present case, amyloid was found in the histopathological examination of both valves. On the other hand, patients on dialysis are more likely to develop AS because of hyperphosphataemia, hypercalcaemia, and hyperparathyroidism. In addition, increase in extracellular fluid volume, anaemia, and increase in cardiac output due to vascular access lead to increased flow velocity and turbulence across the aortic valve in dialysis patients. These mechanisms can lead to fibrosis and aortic valve calcification. It is likely that chronic kidney disease, mineral and bone disorder influence onset and development of AS in dialysis patients.^{7–10}

The 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathies recommend routine echocardiographic controls every 12–24 months in clinical stable patients.¹¹

The 2017 ESC Guidelines for the management of valvular heart disease⁶ recommend for patients with mild aortic stenosis to be reviewed on a yearly basis and echocardiography performed every 2 years.

These recommendations were not followed, presumably due to a lack of cardiac symptoms. The lack of specific cardiac symptoms could be explained by the compensating mechanisms in a young heart of a 40-year-old patient and the low awareness of these symptoms in a patient with reduced mobility due to highly active rheumatic disease and physical limitation due to chronic dialysis.

If the progression had been detected earlier, a better outcome after cardiac surgery would have been probable due to a better overall situation and thus lower surgical risk.

Different mechanisms of the underlying disease should be considered in the fatal post-operative course:

Both Amyloidosis and kidney failure have been discussed in altering vascular permeability.^{12–14} The underlying rheumatic disease was treated with a monoclonal antibody biological drug therapy for several years, which lead to immunosuppression. Still, the patient post-operatively experienced severe SIRS, which lead to additional

capillary leakage. The patient suffered from recurrent respiratory sepsis which lead to weaning failure and abdominal sepsis as potential consequence from enhanced gastrointestinal capillary. Both the patient's acute on chronic kidney failure with need for continuous dialysis leading to electrolyte deterioration and the accompanying LVH in CA are risk factors for arrhythmias. The patient was defibrillated multiple times due to ventricular arrhythmias with cardiogenic shock. Combined, these factors led to severe multiorgan failure and patient's death.

Conclusion

This severe progression of valve degeneration over a short period shows the necessity of regular cardiological monitoring, including echocardiography, for early detection of progression. Due to the further increased risk in patients with restrictive and infiltrative cardiomyopathies and concomitant chronic dialysis we suggest echocardiographic controls in these patients every 6 months.

Lead author biography



David Frumkin was born in 1990 in Berlin, Germany. He completed Medical studies at the Ruhr University Bochum, Germany. Since 2017 intern at the Department of Cardiology and Angiology, Charité - Universitätsmedizin Berlin, Campus Mitte, Germany.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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