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Case Series

Between Charybdis and Scylla—an Odyssey in AL amyloidosis: insights and learnings from a narrative review and case report series

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***Abstract*:** Being "between Scylla and Charybdis" is an idiom derived from Greek mythology to mean "between a rock and a hard place" and clinicians managing amyloid light-chain (AL) amyloidosis often find themselves in this predicament. AL amyloidosis is caused by monoclonal light chains, most commonly produced by CD-38 positive plasma cells in target organs. The disease usually involves significant cardiac and/or renal involvement, but the systemic nature of the disease often leads to variable and non-specific manifestations that can critically delay early diagnosis and treatment. Here, we present a case series reflecting primarily the cardiologist and hematologist perspective to uniquely illustrate key learnings that we believe have the potential to improve diagnosis timelines, treatment initiation, and ultimately improve outcomes for this severe disease. Through our case series, we illustrate that to achieve an accurate diagnosis, a high degree of clinical suspicion is needed, and we stress the important requirement of substantial multi-disciplinary collaboration. Our experience strongly indicates that AL amyloidosis patients presenting with cardiac symptoms need to be identified and treated rapidly, prior to the development of irreversible cardiotoxicity. In addition, patients without significant cardiac involvement may benefit from rapid initial treatment with daratumumab along with cyclophosphamide-bortezomib-dexamethasone, which can render patients eligible for autologous stem cell transplant (ASCT) or in some instances means they can forgo ASCT completely. Increased awareness of the disease is needed among general cardiologists and hematologists, and specialized centers with the relevant expertise should be willing to accept patients for fast-track evaluation as part of their standard procedures, due to the unique contribution they can offer in the clinical management of this life-threatening disease.

Keywords: AL amyloidosis, cardiac amyloidosis, case report, diagnosis, management

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Introduction

Amyloidoses

Amyloidoses are diseases of protein misfolding whereby insoluble amyloid fibrils with a characteristic beta-sheet structure become intertwined and deposited in the extracellular matrix of different tissues and organs.[1] To date, 42 amyloidogenic proteins and associated variants have been linked to human disease,[1] and amyloid deposits can accumulate in the heart, kidney, liver, spleen, and central nervous system, leading to a diverse range of clinical syndromes.[2,3]

Cardiac amyloidosis is the most frequent manifestation of systemic amyloidoses, of which the

two most common types are amyloid light-chain (AL) amyloidosis, caused by the conversion of soluble immunoglobulin light chains into highly organized amyloid deposits, and amyloid transthyretin cardiomyopathy (ATTR-CM), caused by misfolded amyloidogenic transthyretin protein.[3,4] In both cases, amyloid deposited in the extracellular space leads to "stiffening" of the myocardium and depressed cardiac outputs, resulting in increased ventricle wall thickness and diastolic dysfunction.[3–5] Additionally in AL amyloidosis, infiltration of amyloid can lead to angina, myocardial infarction, atrial fibrillation, and increased risk of thromboembolism.[3–5] If detected late, the prognosis of AL amyloidosis can be extremely poor with median survival times in the region of months, meaning when the diagnosis is confirmed it must be treated as a hematological emergency.[3,4,6]

Here, we provide an overview of AL amyloidosis pathophysiology, diagnosis, staging, and current treatments, and present a case series to share key learnings from our personal experience in the complex management of this difficult-to-detect and life-threatening disease.

AL amyloidosis: Clinical manifestations, diagnosis, staging, and management

Disease overview

AL amyloidosis is primarily a plasma cell disorder, whereby aberrant and difficult-to-isolate CD38-positive plasma cell clones within the bone marrow secrete misfolding-prone, amyloidogenic immunoglobulin light chains that infiltrate tissues and can lead to irreversible damage and organ failure.[7] The direct toxicity of the amyloid light chain can result in a rapid disease progression but also means that disease reversal is possible if the toxic precursor is stopped prior to significant organ involvement.

The global incidence of AL amyloidosis is estimated to be 10 cases/million worldwide, with a 20-year prevalence of 51 cases/million, and is the most common of the systemic amyloidoses.[8,9] Most patients are 65 years and older, with a mean age at diagnosis of 64 years, and slightly more males are affected than females.[10] Due to the multi-system nature of the disease, most often involving a cardiac and/or renal component, the manifestations of AL amyloidosis are myriad, variable, and non-specific, which can lead to substantial clinical misinterpretation that can delay diagnosis and treatment.[7] Cardiac involvement is found in at least 50% of cases and is the most important prognostic determinant, and commonly manifests as heart failure with preserved ejection fraction (HFpEF),[11,12] which will progress rapidly through overt left ventricle (LV) dysfunction and reduced ejection fraction (EF) due to the intense cardiac toxicity of the AL amyloidosis protein. Patients often present with dyspnea (at rest or on exertion), palpitations, chest pains, and syncope.[5] Other common signs include nephrotic syndrome, peripheral neuropathy, and organomegaly, which can manifest symptomatically as weight loss, fatigue, edema, carpal tunnel syndrome, erectile dysfunction, and periorbital purpura.[3,5] Diagnosis requires a high degree of clinical suspicion and multidisciplinary collaboration, particularly between cardiologists and hematologists. Usually, once symptoms are manifested, significant organ damage has already occurred, meaning mechanisms to identify subclinical high-risk patients early are needed to help improve outcomes.[7]

The prognosis for AL amyloidosis is historically very poor. Survival rates prior to the availability of effective treatments ranged from ~13 months down to only 6 months in cases of symptomatic cardiac involvement.[13] Significant progress has been made in the identification of prognostic factors, particularly organ biomarkers.[14] Negative outcomes in AL amyloidosis are strongly linked to the extent and severity of heart involvement, and key prognostic indicators are related to cardiomyocyte damage (elevated cardiac troponins), cardiac dysfunction (increased N-terminal pro-brain natriuretic peptide (NT-proBNP)), and amyloid load (septum thickness).[14,15] After the heart, the kidney is the second most affected organ, with proteinuria (albuminuria) a key marker of kidney dysfunction in AL amyloidosis. This precedes a reduction in estimated glomerular filtration rate (eGFR), and both are important in predicting renal outcomes.[16,17] Plasma cellular factors also have considerable prognostic value, including free light chain (FLC) quantification systems that can measure the amyloid precursor, and the difference between involved and uninvolved FLC (dFLC) can be used in disease staging and reports on organ involvement. A

detectable increase of FLCs has been shown to precede the development of AL amyloidosis symptoms for at least 4 years,[18] which offers promise for potential screening programs to aid early detection. Additional prognostic cellular factors include measurements of plasma cellular burden and fluorescence in situ hybridization (FISH) to look for genetic translocations, particularly *t*(11;14), which is a hallmark of AL amyloidosis.[14]

Diagnosis

Suspicion of AL amyloidosis is complicated by the fact that myriad non-specific symptoms can be easily misinterpreted, consistently leading to a delay in diagnosis.[19] Even in patients with known pre-existing plasma cell dyscrasia (e.g., monoclonal gammopathy of undetermined significance (MGUS)), AL amyloidosis diagnosis among experienced hematologists can take up to a year.[20] Differential diagnosis is challenging because of the potential involvement of different specialties and the high risk of missed diagnosis; however, demonstrating cardiac involvement is critical given the heart is the most commonly affected organ and closely linked to survival outcomes. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement can be highly accurate in detecting amyloidosis.[21]

Once AL amyloidosis is suspected, establishing a monoclonal component is necessary by measuring the serum kappa/lambda FLC ratio as well as performing serum and urine immunofixation electrophoresis to detect abnormalities.[19] If these are negative, then AL amyloidosis can usually be ruled out and diagnostic workup for other amyloidoses should be performed, such as cardiac scintigraphy. Once a monoclonal component is established, tissue diagnosis to detect amyloid deposits in abdominal fat, bone marrow, and/or the minor salivary gland is usually sufficient, without the need for biopsy of the primary affected organ.[19,22] Congo red staining with polarization or fluorescence microscopy, or immune-electron microscopy using commercial antibodies, can be highly effective methods of detecting amyloid; immunohistochemistry using standard light microscopy with custom antibodies can also be effective but requires high-specificity antibodies and is best performed at specialized centers.[23–25] Staining of multiple tissues can be useful to increase diagnostic sensitivity—abdominal fat combined with bone marrow or salivary gland staining reaches ~90% sensitivity at referral centers.[19] Mass spectrometry is highly effective at detecting major fibril proteins, as well as numerous tissue components that together create a typical proteomic "amyloid signature," and this approach is now favored by the Mayo Clinic as the "gold standard" for amyloid tissue typing, achieving nearly 100% sensitivity.[24,26]

Unfortunately, most patients are diagnosed only after they become symptomatic, generally signaling organ involvement. However, it is possible to identify some "red flags" that may aid pre-symptomatic diagnosis for AL amyloidosis among patients with MGUS with an abnormal FLC ratio, including raised NT-proBNP/BNP (confirmed with cardiac MRI), albuminuria, and raised alkaline phosphatase. It has been estimated that such screening should detect one patient with MGUS progressing to AL amyloidosis for every 7–10 progressing to multiple myeloma (MM). Increased awareness of AL amyloidosis, coupled with collaboration among hematologists and cardiologists, is needed to improve the rates of early detection and diagnosis, when outcomes are more likely to be positive.

Disease staging

Staging for AL amyloidosis is primarily based on the severity of heart damage, as this is generally the most important prognostic factor in predicting survival.[27] The original staging system (Mayo Clinic 2004) utilized cardiac troponin T (cTnT) or I (cTnI) and NT-proBNP to stratify patients into stages I–III.[28] Troponin is traditionally used in cardiology for detection of ischemia and infarction; however, in the context of AL amyloidosis, it is a marker of myocardial necrosis due to direct toxicity of the FLC.[29] Staging modifications include the European separation of stage III into IIIA and IIIB depending on NT-proBNP level (and in some cases systolic blood pressure),[30–32] and the Boston University substitution of NT-proBNP with the more widely available BNP (Table 1).[33] Mayo Clinic updated their staging in 2012 to account for clonal characteristics of the pathogenic plasma cell clone and incorporated dFLC (Table 1).[34] Secondary to cardiac staging, a separate staging system has been developed based on renal function and relies on proteinuria

Table 1. Overview of the AL amyloidosis cardiac staging systems.

Mayo Clinic 2004		
Stage	*Biomarker (threshold)*	*Determination*
I	cTnT (0.035 µg/L)[a]	Both markers below the threshold
	NT-proBNP (332 ng/L)[b]	
II	cTnT (0.035 µg/L)[a]	One marker above the threshold
	NT-proBNP (332 ng/L)[b]	
III	cTnT (0.035 µg/L)[a]	Both markers above the threshold
	NT-proBNP (332 ng/L)[b]	
Modified/European Mayo Clinic 2004		
IIIA	cTnT (0.035 µg/L)[a]	Both markers above the threshold, but NT-proBNP <8500 ng/L
	NT-proBNP (332 ng/L)	
IIIB	cTnT (0.035 µg/L)[a]	Both markers above the threshold, but NT-proBNP ⩾8500 ng/L
	NT-proBNP (332 ng/L)	
Mayo Clinic 2012		
I	cTnT (0.025 µg/L)[a,c]	All markers below the thresholds
	NT-proBNP (1800 ng/L)	
	dFLC (180 mg/L)	
II	cTnT (0.025 µg/L)[a,c]	One marker above the threshold
	NT-proBNP (1800 ng/L)	
	dFLC (180 mg/L)	
III	cTnT (0.025 µg/L)[a,c]	Two markers above thresholds
	NT-proBNP (1800 ng/L)	
	dFLC (180 mg/L)	
IV	cTnT (0.025 µg/L)[a,c]	All three markers above thresholds
	NT-proBNP (1800 ng/L)	
	dFLC (180 mg/L)	

[a]Or cTnI (<0.1 µg/L); [b]Boston University reported BNP could be used at a threshold of 81 pg/mL, which correlated well with the 332 ng/L NT-proBNP threshold; [c]Or ultra-sensitive cTnT (<40 µg/L).
Renal staging can also be used if there is a predominant renal component as follows: Stage I, both proteinuria ⩽5 g/24 h and eGFR ⩾50 mL/min per 1.73 m^2; stage II, either proteinuria >5 g/24 h or eGFR <50 mL/min per 1.73 m^2; stage III: both proteinuria >5 g/24 h and eGFR <50 mL/min per 1.73 m^2
BNP, brain natriuretic peptide; cTnT, cardiac troponin T; cTnI, cardiac troponin I; dFLC, difference between involved and uninvolved free light chain; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.

and eGFR to predict the risk of renal outcomes.[16] Proteinuria is associated with increased preservation of renal function, while an early decrease in eGFR predicts poor renal outcomes. The renal staging system can be useful in predicting end-stage renal disease and progression to dialysis but has less utility in predicting survival outcomes.

Disease course and treatment

AL amyloidosis belongs to the same group of "plasma cell neoplasms" as MM (and MGUS),[35] and there can be a co-existence of disease whereby 10%–15% patients with AL amyloidosis also have MM.[36] However, the disease course radically differs since MM is a slowly progressing disease,[37] compared with AL amyloidosis, which is essentially a cardiotoxic disease with rapid clinical and lethal progression.[7] As such, the approach to optimizing treatments in MM and AL amyloidosis is very different, with a more aggressive, proactive, and time-sensitive approach to treatment required in AL amyloidosis. Early, rapid identification and treatment of patients drastically reduces irreversible cardiac complications, thereby improving prognosis in AL amyloidosis.[19] Standard-of-care treatment for MM is autologous stem cell transplantation (ASCT), but only a minority (~20%) of patients with AL amyloidosis are eligible for ASCT due to the inherent cardiac involvement that substantially increases the risks associated with transplantation to a prohibitive level.[19,38] However, outcomes in patients who are eligible for, and receive, ASCT before cardiac involvement is prohibitive, have a much better disease-free prognosis.[19,38]

Alternatives to ASCT in AL amyloidosis have included regimens consisting of chemotherapy, immunomodulatory agents, and proteasome inhibitors (e.g., cyclophosphamide-bortezomib-dexamethasone (CyBorD)), all of which have been used with reasonable success.[39] More recently, the addition of the anti-CD38 daratumumab to CyBorD (dara-CyBorD) resulted in deeper and more rapid hematological responses than CyBorD alone, and dara-CyBorD is the first formally approved treatment for AL amyloidosis.[39,40] In patients without significant neuropathy who are ineligible for ASCT, dara-CyBorD is recommended by the European Society of Haematology and International Society of Amyloidosis (ISA) as first-line treatment.[39]

The following case studies highlight two important learnings in the management of AL amyloidosis. First, patients showing symptoms of cardiac involvement need to be identified and treated rapidly, prior to the progression to irreversible cardiac damage. Second, patients may benefit from initial, rapid treatment with dara-CyBorD, which may render them eligible for ASCT (if they do not have substantial cardiac involvement), or in some cases mean they can forgo ASCT altogether.

Case study key learnings

Case study 1

Presentation. A 59-year-old female patient with a history of hypertension presented with severe back pain and right rib pain, along with newly diagnosed renal impairment. Three months prior, she experienced a spontaneous tibial fracture.

Laboratory markers. Laboratory tests revealed hemoglobin 7.8 g/dL, platelet count 250,000/mm^3, white blood cell count 6.5/mm^3, creatinine 304 µmol/L (improved to 102 µmol/L with hydration), uric acid 606 µmol/L, calcium 3.45 mmol/L, erythrocyte sedimentation rate 22 mm/h, low levels of immunoglobulin G (IgG) and immunoglobulin M. β2-microglobulin 11 mg/L, albumin 3.3 g/L, 24-h urine 0.8 g/24 h, cTnT 30 ng/L and NT-proBNP 1174 pg/ml. Serum FLC analysis revealed a kappa/lambda ratio 0.013 (kappa 24.4 mg/L; lambda 1810 mg/L). Serum protein electrophoresis confirmed monoclonal gammopathy (lambda FLC 1100 mg/L), as did urine protein electrophoresis (Bence Jones protein).

Investigations. Bone marrow aspiration and biopsy showed a relatively cellular marrow with an overall estimated cellularity of 50%. There was background trilineage hematopoietic maturation with focal collections and interstitial infiltration by atypical plasma cells and plasmacytoid cells comprising ~20% of cellularity, consistent with plasma cell myeloma. There was no morphologic evidence of amyloidosis by trephine biopsy and cytogenetics using a myeloma FISH panel were not suggestive of *t*(11;14). Abdominal wall fat biopsy revealed fibroadipose tissue with amyloid deposition consistent with amyloidosis (Congo red positive) and the skeletal survey showed diffuse osteopenia and multiple scattered lytic

lesions involving the calvaria bones and extremities. Whole-body MRI revealed diffuse osseous lesions, and acute/subacute anterior wedge fracture of L2 as well as multi-level vertebral superior and inferior end-plate depression. Abdominal ultrasound revealed an enlarged liver (~18 cm), with a homogeneous appearance and minimal mild biliary radicles dilatation; the spleen appeared normal size. 2D-echocardiogram showed an EF >55%; the trans-mitral spectral Doppler flow pattern was suggestive of impaired LV relaxation. There were no definitive findings of cardiac amyloidosis.

Red flags and diagnosis. Red flags in this patient that warranted investigation for AL amyloidosis included cardiac symptoms (raised cardiac biomarkers) in a patient with MM.

Based on clinical findings and diagnostic investigations, the working diagnosis was MM with AL amyloidosis.

Treatment and outcomes. The patient received seven cycles of dara-CyBorD and post-treatment evaluation showed serum FLC ratio 1.327 (lambda FLC 7.74 mg/L); cTnT 11 ng/L; NT-proBNP 127 pg/mL. Bone marrow biopsy showed cellular bone marrow with active tri-lineage hematopoiesis, with no immunomorphological evidence of MM. The patient underwent ASCT with melphalan 200 mg/m^2 conditioning and was prescribed maintenance lenalidomide 10 mg; she continues to be in remission.

Clinical learnings. This case highlights several key points: although echocardiogram results were inconclusive for a cardiac amyloidosis diagnosis, discussion with the multidisciplinary team concluded the reason for impaired LV relaxation was highly likely to be from amyloidosis involvement. Of note, the patient had renal impairment which improved to normal after hydration, indicating that cardiac biomarker elevation was likely related to cardiac involvement rather than secondary to renal impairment. The elevated cardiac biomarkers raised concerns about proceeding with ASCT due to the likelihood of toxicity; however, importantly, the use of the dara-CyBorD combination effectively normalized cardiac biomarkers, rendering the patient eligible for ASCT.

In patients with plasma cell disorders, cardiac assessment with echocardiogram and biomarkers is essential and the frequency should be optimized. Although symptoms could be attributed to severe anemia, they are also likely to be related to HF and cardiac toxicity. While anemia is common in patients with plasma cell dyscrasia, proactively analyzing cardiac function and biomarkers is essential. Importantly, a normal EF does not exclude cardiac involvement, since a detailed diastolic assessment can confirm a HFpEF phenotype, at an earlier stage before the EF rapidly drops.

Case study 2

Presentation. A 67-year-old male patient with a history of coronary artery bypass graft (6 years prior) for coronary artery disease (CAD) presented after being seen by multiple physicians (including cardiologists and pulmonologists) for extreme fatigue and weakness. The patient had a cerebrovascular accident requiring embolectomy 6 months prior and had experienced four recurrent pleural effusions post-thoracentesis, with workup performed on multiple occasions in different facilities; cytology was negative. A recent chest computed tomography showed a right pleural effusion and moderate-to-large left pleural effusion with underlying subsegmental collapse, while a recent echocardiogram showed normal LV systolic function with an EF of 55%–59% and LV hypertrophy (LVH). The patient was not known to be hypertensive but had chronic renal insufficiency that had worsened over the last 2 years.

Laboratory markers. Blood markers showed hemoglobin 128 g/L, red cell distribution width 14.9% and monocyte count 10.4%. Laboratory tests showed glucose 6.6 nmol/L, urea 16.5 nmol/L, creatinine 231 µmol/L, osmolality 299 mOsmol/kg, and chloride 97 nmol/L. Urine immunofixation was negative, protein urea 0.5 g, serum electrophoresis showed total protein 60 g/L, albumin 33.5 g/L, alpha-1 (5.1%) and alpha-2 (13.0%) globulins. Cardiac biomarkers were cTnT 0.049 ng/mL and NT-proBNP 4110 ng/L. Serum FLC analysis revealed a kappa/lambda ratio of 0.4902 (kappa 54.9 mg/L; lambda 1120 mg/L).

Investigations. Bone marrow aspirate smears showed ~2% plasma cells (CD45-, CD19-, and CD56-negative; CD38-, CD138-, and CD117-positive). Plasma cells comprised ~20% of bone marrow cellularity and flow cytometry analysis showed cytoplasmic monoclonal lambda-restricted plasma cells. The morphologic and immunophenotypic findings were consistent with bone marrow involvement by plasma cell neoplasm. Congo red staining on bone marrow was negative. FISH/cytogenetics were normal. Abdominal fat pad biopsy had features consistent with amyloidosis; Congo red staining was positive, and mass spectrometry revealed a peptide signature consistent with AL (lambda)-type amyloid deposition. 2D-echocardiogram estimated EF at 50%–55%; LV cavity size and systolic function were normal, but wall thickness appeared moderately increased consistent with concentric LVH. The myocardium had a speckled appearance suggestive of cardiac amyloidosis, but the pyrophosphate (PYP) scan was not indicative of ATTR-CM.

Red flags and diagnosis. Red flags in this patient that warranted further investigation for AL amyloidosis included raised cardiac biomarkers, echocardiogram showing LVH with discordance (normal LV systolic function), and worsening chronic renal insufficiency.

The diagnosis was stage IIIa AL amyloidosis (AL lambda-restricted with cardiac and suspected renal involvement).

Treatment and outcomes. The patient received six cycles of dara-CyBorD, followed by single-agent daratumumab maintenance therapy (currently ongoing at 17 cycles). A follow-up echocardiogram showed improvements in both mild LVH and speckle tracking. Furosemide and spironolactone requirements both improved (furosemide 80 mg BID at diagnosis reduced to 20 mg every other day; spironolactone reduced from 100 mg daily at diagnosis to 25 mg daily). Performance status also markedly improved.

Clinical learnings. This case presented a difficult diagnosis primarily because FLCs were not highly raised, indicating that even at low concentrations, amyloidogenic light chains are capable of rapid deposition leading to intense toxicity. The suspicious findings of LVH and suggestive echocardiogram profile in the absence of any history of hypertension were "red flags" for amyloidosis. ATTR was initially suspected, but the negative PYP scan coupled with clonal lambda restriction and plasmacytosis on marrow, and amyloid confirmation on fat pad biopsy based on mass spectrometry confirmed the AL amyloidosis diagnosis. In this case, organ response assessment was challenging, and patient response was based on improvement in cardiac and functional status, no recurrence of the pleural effusion, and amelioration of diuretic use. This case highlights the crucial importance of maintaining a high index of clinical suspicion and pursuing a fat pad or organ-directed biopsy with amyloid typing to establish a diagnosis. More sensitive measurement assays like mass spectrometry can be pivotal in cases like this.

Case study 3

Presentation. A 56-year-old male patient with a history of well-controlled type 2 diabetes (15 years) and dyslipidemia presented with progressive abdominal pain, early satiety, and weight loss over 1 year. Frequent falls were reported, as were lower limb swelling, frothy urine, and erectile dysfunction. The patient had been taking metformin 500 mg BID and rosuvastatin 10 mg OD. On examination, he appeared cachectic and was afebrile. Blood pressure 84/58 mmHg, pulse 84 beats/min, O_2 saturation 100% (room air) and he had an Eastern Cooperative Oncology Group performance status of 1–2, with evidence of lower limb edema. Importantly, the patient had recently initiated fludrocortisone 0.1 mg OD for hypotension. The patient's orthostatic hypotension and gastrointestinal symptoms, alongside symptoms indicative of autonomic and peripheral neuropathy, were considered disproportionate to his diabetes.

Laboratory markers. Laboratory tests showed creatinine 57 µmol/L, albumin 16 g/L, calcium 1.97 mmol/L, total protein 39 g/L, lactate dehydrogenase 185 units/L, and 24-h urine protein 2.27 g/24 h. Serum FLC analysis showed a kappa/lambda ratio of 0.2 (kappa 194 mg/L; lambda 831 mg/L). Cardiac biomarkers were NT-proBNP 151 ng/L and cTnT < 0.01 µg/L.

Investigations. Electrocardiogram (ECG) revealed a normal sinus rhythm but with low voltage, and the echocardiogram showed normal LV size and

function (EF > 55%), no septal wall thickening, and normal pulmonary artery pressure. Bone marrow results revealed 20%–22% clonal plasma cells that were CD38-, CD138-, and CD56-positive, and lambda restriction, while cytogenetic analysis showed a normal diploid karyotype. Congo red staining of a renal biopsy was positive, but proteomic amyloid typing was not done.

Red flags and diagnosis. Red flags of AL amyloidosis warranting further investigation included frequent falls with lower limb edema, proteinuria, low-voltage ECG, orthostatic hypotension, gastrointestinal symptoms, and symptoms indicative of autonomic and peripheral neuropathy.

AL amyloidosis was diagnosed upon referral; autoimmune glomerulonephritis and cryoglobulinemia were considered and ruled out.

Treatment and outcomes. The patient received intravenous dara-CyBorD (subcutaneous daratumumab was not available) for six cycles followed by daratumumab for 18 months. A complete response occurred after cycle 1; after cycle 2, appetite, diarrhea, and dizziness improved; after cycle 3, fludrocortisone was stopped, and blood pressure started to stabilize. Treatment was completed in October 2022 and 1 year later the patient's status had largely returned to normal (apart from continuing erectile dysfunction); laboratory evaluation showed a white blood cell count of 8.3/mm^3, hemoglobin 173 g/L, platelet 225,000/mm^3, creatinine 82 µmol/L, total protein 61 g/L, and albumin 36 g/L. Serum protein electrophoresis showed no M band, urine was Bence-Jones protein negative, IgG 7.6 mg/dL, and serum FLC assay ratio 0.86 (kappa 185 mg/L; lambda 206 mg/L).

Clinical learnings. It is important to note that autonomic dysfunction could have been assumed to be related to the patients' diabetes and overlooked; however, its improvement with treatment indicates that it was related to AL amyloidosis. The unremarkable echocardiogram and mild elevation of NT-proBNP highlight that the patient was diagnosed and treated early, prior to severe cardiac involvement.

Case study 4

Presentation. A 49-year-old male patient presented in April 2021 with fatigue and baseline shortness of breath, particularly during moderate exertion (New York Heart Association (NYHA) class II–III). Symptoms had been ongoing for 4 months and the patient experienced occasional orthopnea, requiring at least two pillows to sleep comfortably. His medical history was unremarkable and did not include cardiovascular risk factors; he was healthy and exercised twice a week. Weight 71 kg and height 1.72 cm (BMI 24 kg/m^2). Upon initial evaluation, symptoms were attributed to a recurrent supraventricular tachycardia (SVT) arrhythmia; SVT ablation was performed but was complicated by a complete heart block requiring immediate VVI pacemaker implantation. The patient had a transthoracic echocardiogram that was considered "normal" for his age despite high NT-proBNP (>10,000 ng/L); troponins were not examined, and his renal profile was considered borderline. The patient continued to deteriorate with worsening HF symptoms despite treatment with a pacemaker and diuretics; he sought a second opinion in July 2021. This evaluation showed persistent arrhythmia (labeled persistent atrial fibrillation with paced rhythm), while the echocardiogram showed normal LV size, mild LVH, moderate LV systolic dysfunction, EF ~40%, raised LV filling pressure with a restrictive pattern, moderate systolic pulmonary hypertension, mildly dilated right ventricle (RV) size and mildly reduced function, as well as moderate bi-atrial enlargement and small pericardial effusion. Restrictive cardiomyopathy was suspected.

Laboratory markers. NT-proBNP was substantially elevated (>15,000 ng/L), and ultrasensitive cTnT was elevated (>100 ng/L); serum and urine electrophoresis revealed M component (1.8% of total serum proteins and 37% of the gamma globulins) and low albumin, and the patient was referred to hematology for additional investigations, including bone marrow and FLC analyses. Results indicated a very high FLC assay ratio of 122.8 (kappa > 90,000 mg/L).

Investigations. Bone marrow biopsy was positive for Congo red staining, and plasma cells comprised 60% of cellularity.

Red flags and diagnosis. There were multiple cardiac red flags in this patient, including atrial fibrillation/persistent arrhythmia, pacemaker

implantation, raised biomarkers, heart failure with AV block, discordant echocardiogram, and intolerance to standard HF therapies.

A diagnosis of systemic AL amyloidosis with severe cardiac involvement was made (12 months after initial assessment and 16 months after symptom onset).

Treatment and outcomes. Initial treatment with two cycles of CyBorD led to no clinical improvement; thus, the patient was referred to our tertiary center in September 2021. Repeated bone marrow examinations consistently demonstrated ~60% plasma cells. Upon presentation, the FLC ratio was 164 (kappa 1100 mg/L, lambda 6.7 mg/L) and bone marrow biopsy was Congo red-positive, while immunohistochemistry confirmed kappa FLC. Echocardiogram confirmed previous findings with severe cardiac involvement and typical relative apical sparing on global longitudinal strain (GLS) pattern (global GLS –9%); prognostic classification was IIIb (blood pressure 100/65 mmHg), and biomarkers were elevated (NT-proBNP levels ~15,000 ng/L and cTnT levels 100 ng/L).

The patient developed a large left pleural effusion that was refractory to high-dose diuretics, (later suspected to be due to AL amyloidosis). AL amyloidosis work-up revealed the involvement of several organs including the liver (elevated alkaline phosphatase and bilirubin) and gut (Congo red-positive duodenal biopsy). Surprisingly, the kidneys were unaffected with a normal renal profile and no obvious nephrotic syndrome. Multidisciplinary discussions confirmed the critical situation and the patient ineligibility for ASCT due to severe cardiomyopathy. Despite limited data regarding daratumumab at the time, the patient's treatment was transitioned from CyBorD to dara-CyBorD. After a few cycles, his overall clinical condition substantially improved (apart from ageusia and abdominal pain); his pacemaker was upgraded, and he had cardiac resynchronization therapy implantation that improved his LV contractility. His EF was ~50% and GLS −12%. He had moderate pulmonary hypertension and mildly raised filling pressure and underwent pleurocentesis for pleural effusion. The patient completed six cycles of dara-CyBorD, and his organ response was parallel to his hematological response.

As of June 2024 (~4.5 years after symptoms onset, 3 years from treatment initiation, and 1 year after switching healthcare provider), the patient has substantially improved at all levels. He reports it being completely asymptomatic. He is currently receiving furosemide 40 mg BID, spironolactone 25 mg OD, apixaban 5 mg BID (due to persistent atrial fibrillation) and is receiving one dose of daratumumab every month. The most recent laboratory evaluations demonstrate notable improvements, with NT-proBNP levels ranging from 1000 to 1500 ng/L and an FLC ratio of 2.5. His quality of life has significantly improved, and he has follow-up cardiology and hematology appointments every 6 months.

Clinical learnings. This case highlights that although early diagnosis and treatment of systemic AL amyloidosis is usually needed to obtain a positive clinical response, excellent outcomes can be achieved after appropriate and rapid treatment in patients with a late diagnosis who are already showing signs of severe cardiac involvement. The case further demonstrates that aggressive hematological treatment in young, otherwise healthy patients can help to avoid cardiac transplantation or cardiac death. Importantly, weekly follow-up should monitor hematological (FLC) and organ (BNP) responses and allow treatment protocols to be adjusted in the event of a rapid response. Finally, this case suggests that VVI pacing can be harmful in some patients, particularly those with LV dysfunction and a restrictive pattern, and a personalized decision regarding cardiac resynchronization therapy pacemaker implantation is advisable.

Case study 5

Presentation. A 38-year-old female patient with a medical history of beta-thalassemia minor/intermedia, bilateral carpal tunnel syndrome, and cutaneous amyloidosis presented to the emergency department in November following a vasovagal episode.[22]

The patient reported multiple episodes of exertional dyspnea and chest tightness. She reported no known CAD risk factors and no family history of CAD. She also reported blurring of her vision and diplopia. The patient could not tolerate angiotensin-converting enzyme inhibitors at the lowest dose due to orthostasis and hypotension with

syncope. Further symptomatic developments included loss of consciousness with a tingling left arm but no evidence of stroke, edema, and fluid overload requiring treatment with diuretics.

Laboratory markers. cTnT and NT-proBNP levels were elevated (0.074 µg/L and 1,556 ng/L, respectively) without any indication of HF. Hemoglobin was 92 g/L, and hematocrit was 29%. FLC ratio was 0.01 (kappa 7.93 mg/L; lambda 1217 mg/L); serum immunofixation revealed two discrete lambda FLC bands, while urine immunofixation revealed an FLC ratio of 0.02 (lambda 902 mg/L). Blood pressure ranged from 88–92/50–54 mmHg.

Investigations. ECG showed low voltage but no signs of acute coronary syndrome or arrhythmia. The patient was admitted for telemetry monitoring and had another syncopal attack while on telemetry without any significant arrhythmia. Computed tomography angiogram cardiac protocol showed normal coronary arteries with a calcium score of 0. To further evaluate diplopia and blurring of vision, she had a brain MRI, which was negative for acute ischemic or hemorrhagic process; however, white matter signal intensity foci were noted in both supratentorial cerebral hemispheres that do not favor demyelinating process. Suggested differential diagnoses were vasculopathy, hypertension, or migraine.

Sinus tachycardia and marked diffuse low voltage were evident by ECG; this was discordant with the echocardiogram showing mild concentric LVH with normal EF (54%) and increased LV wall echogenicity. There was a decreased GLS pattern (−11.8%) with relative apical sparing. Bone marrow biopsy revealed 25% plasma cells with lambda light chain immunoglobulins and was Congo red negative; skin biopsy was Congo red positive with fat pad biopsy also confirming amyloidosis. There was patchy late gadolinium enhancement of fusiform mid-myocardial lateral wall base by cardiac MRI as well as inferior interventricular groove enhancement (base to mid ventricle); findings of epicardial enhancement of the lateral wall, epicardial RV free wall, and septal epicardial enhancement were consistent with myocarditis. A nuclear medicine PYP scan was equivocal for AL amyloidosis or early ATTR amyloidosis. The patient later presented with spontaneous periorbital ecchymosis.

Red flags and diagnosis. This patient presented with several classic red flags for amyloidosis including carpal tunnel syndrome, intolerance to standard HF therapies, LVH with increased LV wall thickness, low voltage ECG, loss of consciousness with tingling left arm but no evidence of stroke, and edema and fluid overload requiring treatment with diuretics.

AL amyloidosis with cardiac involvement, secondary to light chain myeloma.

Treatment and outcomes. The patient was initiated on CyBorD therapy; however, her EF dropped to 36% after 70 days; this occurred alongside increased myocardial echogenicity, GLS −10.7%, grade III LV diastolic dysfunction, and biatrial and biventricular enlargement. The patient was admitted to the hospital after the third cycle of chemotherapy with worsening HF and was COVID-19 positive; echocardiogram revealed EF 33% with GLS −6% and NT-proBNP had markedly increased (>5000 ng/L). One week later the patient was readmitted to the hospital with worsening HF and hypokalemia; she discharged herself against medical advice and experienced a sudden cardiac arrest which led to her passing away in April, merely 5 months after presenting to the emergency department.

Clinical learnings. This case highlights potentially conflicting diagnostic modalities that need to be integrated to establish the correct diagnosis. The clinical clues for amyloidosis were numerous in this patient but were unfortunately missed due to the fractured nature of the medical referral system. The rapid progression of her cardiac involvement is typical in AL amyloidosis due to the direct tissue toxicity and persistent increase in circulating FLC. The equivocal PYP scan together with the discordant echocardiogram results showing biventricular hypertrophy and GLS with an apical sparing pattern, were a strong clinical clue to the cardiac amyloidosis diagnosis. These cardiac findings paired with physical findings and abnormal FLC in a patient with progressive HF and elevated NT-proBNP strongly point to AL amyloidosis. Clinicians should consider that the cardiac MRI results shown in this case can easily be misinterpreted as myocarditis.

AL amyloidosis is a multisystem disorder that needs to be globally integrated for early recognition

and rapid initiation of therapy. AL amyloidosis is a true hematological emergency as demonstrated by the very rapid and fatal progression of LV dysfunction and sudden death. At the time of this patient, daratumumab was not yet a standard-of-care treatment despite its significant benefit in survival and reduction in mortality.

Case study 6

Presentation. A 48-year-old female patient presented with sudden onset left-sided weakness and was found to have right internal carotid artery and right middle cerebral artery occlusion. The patient reported a 1-year history of shortness of breath and syncopal attacks.

Laboratory markers. Investigations showed a steady elevation of troponin, normal creatinine kinase, myocardial band, and elevated NT-proBNP. Serum immunofixation showed IgG monoclonal protein with lambda chain specificity, a kappa/lambda ratio of 0.03 (lambda 322.39 mg/L), and urine immunofixation showed lambda FLC specificity. A hematological workup revealed an unremarkable coagulation profile, with normal karyotyping. Bone marrow flow cytometry identified a small population of lambda-restricted plasma cells, while bone marrow aspirate revealed lambda FLC-restricted clonal plasma cells with $<10\%$ marrow cellularity.

Investigations. Echocardiography demonstrated increased LV wall thickness with apical sparing, biatrial enlargement, EF 42%, and abnormal GLS pattern, suggestive of cardiac amyloidosis. Cardiac investigations revealed elevated troponin with normal LV systolic function, grade 3 diastolic dysfunction, and restrictive pattern. These findings were attributed to suspected atrial arrhythmia and bisoprolol was initiated. ECG showed low voltage discrepant to LV wall thickness on the echocardiogram, with occasional premature ventricular complex. Cardiac MRI revealed diffuse global myocardial delayed enhancement involving both LV and RV myocardium and both atrial walls. These findings were compatible with systemic infiltrative diseases, such as cardiac amyloidosis.

Red flags and diagnosis. The presence of elevated cardiac biomarkers, classic amyloidosis findings on echocardiography (increased LV wall thickness with apical sparing and abnormal GLS pattern), and low voltage on ECG led to the suspicion of amyloidosis and prompted the work-up for AL amyloidosis.

Abdominal fat pad biopsy revealed no amyloidosis and had negative Congo red staining. However, after 2 months of therapy, a myocardial biopsy was conducted that showed mild edema, mild interstitial fibrosis, and was strongly positive for Congo red staining suggestive of amyloid deposition, confirming cardiac amyloidosis.

Treatment and outcomes. The patient was initiated on anticoagulation therapy given her high risk of intracardiac thrombus formation, heart failure medication was optimized (bisoprolol fumarate, spironolactone, and valsartan), and chemotherapy for amyloidosis was initiated with CyBorD. The patient continued to receive weekly treatment with CyBorD as an outpatient, without significant toxicity. Three months into chemotherapy, cardiac MRI showed an increase in the amount of delayed enhancement, while echocardiography showed progressive worsening noted by an increase in global eliminated LV myocardial strain from -12.20% to -5.69%, with a decline of overall EF. Myeloma biomarkers had no significant drop in value, indicating minimal response to CyBorD therapy. Daratumumab was initiated to lower the disease burden and decrease further cardiac damage, alongside multidisciplinary discussions regarding eligibility for ASCT if cardiac function improved. Following 6 months of daratumumab treatment, the patient showed serial improvements; NYHA functional class status improved from III to I, and the six-minute walk test improved from 341 to 405 m without desaturation. A significant drop in NT-proBNP was seen, and repeat echocardiography showed stable global strain and improvement in EF to 47%.

At the time of writing, the patient continues to do well and is regularly followed up as an outpatient. One year following diagnosis, the patient completed dara-CyBorD treatment, and the latest EF was 37% with residual scarring of the myocardium.

Clinical learnings. Patients with AL amyloidosis and sinus rhythm can develop atrial thrombosis due to impaired atrial function and low cardiac output, particularly when echocardiography reveals minimal or absent mechanical activity. Initiation of anticoagulation even in sinus rhythm prevents cardioembolic events, and it is important

to consider thrombotic risk in cardiac amyloidosis patients in whom intracardiac thrombotic events can frequently occur.[41,42]

For patients with cardioembolic events and rapid progression of LV dysfunction, clinical suspicion should start with echocardiographic findings of LVH, severe LV diastolic dysfunction grade III, and discordance with low-voltage ECG and conduction abnormalities. Despite cardiac involvement, the decision to treat with conventional therapy and delayed utilization of daratumumab resulted in a very rapid progression of myocardial damage within 3 months.

The abdominal fat pad biopsy was deceptive, early utilization of endomyocardial biopsy would have led to the earlier introduction of daratumumab. Rapid clearance of FLCs after initiation of daratumumab, particularly when there was minimal response to conventional CyBorD therapy, paralleled the rapid improvement of BNP and troponin, and predicted the patient's final cardiac function.

Case study 7

Presentation. A 60-year-old female patient presented with a history of chronic kidney disease, type II diabetes mellitus, dyslipidemia, hypothyroidism, HFpEF, and who 1 year prior underwent transcatheter aortic valve replacement (TAVR) for aortic stenosis; however, despite a successful TAVR, the patient continued to progressively worsen over time. The patient was referred for progressive cardiomyopathy, her cardiac MRI was highly diagnostic for cardiac amyloidosis with an abnormal T1 map and failure to null with late gadolinium enhancement. She also had abnormal immunofixation studies. She described a history of shortness of breath on minimum exertion with intermittent chest pain, and palpitation of several weeks' duration, and was admitted for optimization of HF medication and further investigations.

Laboratory markers. Laboratory investigations showed NT-proBNP 13,761 ng/L, creatinine 106 μmol/L, potassium 3.9 mmol/L, troponin 0.09 mcg/L, normal liver function tests, and hemoglobin 107 g/L. During hospitalization, serum immunofixation showed a kappa/lambda ratio of 23.25 (kappa 608.09 mg/L). The patient underwent an abdominal fat pat biopsy which contained kappa FLC and was Congo red positive.

Investigations. Clinical examination showed traced jugular venous pulse at 11 cm at the level of the mandible, chest crackles, and significant lower limb edema. ECG low voltage was negative for dynamic ST-T changes and conduction abnormalities. Initial echocardiography showed EF 45% with marked LVH and reduced global strain with apical sparing, which was highly suspicious of cardiac amyloidosis. LV diastolic function was grade II, and there was moderately severe tricuspid valve regurgitation. Bioprosthetic aortic valve was noted without valvular or paravalvular leak. The patient also had a patent foramen ovale detected by saline contrast with Valsalva. During hospitalization, the patient complained of difficulty swallowing which was more prominent with solid foods, as well as some changes to her voice. Examination of her neck showed a significant goiter and a thyroid ultrasound was suggestive of thyroiditis. The patient was evaluated by an endocrinology team, and further laboratory tests were conducted; her levothyroxine dose was adjusted based on thyroid function tests.

Red flags and diagnosis. In this patient, her red flags included a history of chronic kidney disease, TAVR for aortic stenosis that progressively worsened over time, and a cardiac MRI with an abnormal T1 map and failure to null with late gadolinium enhancement.

The patient underwent a PYP scintigraphy scan that was reported as grade 2 cardiac uptake, heart-to-contralateral lung ratio of 1.27, and was deemed equivocal for TTR amyloidosis. Alongside the Congo red-positive abdominal fat pad biopsy, the patient underwent bone marrow biopsy, and flow cytometry of bone marrow aspirate showed a small population of kappa-restricted plasma cells. The bone marrow revealed hypercellular marrow with maturing trilineage hematopoiesis, with approximately 15% of bone marrow cellularity being of clonal plasma cell origin with kappa light chain immunoglobulins.

Treatment and outcomes. The patient was initiated on CyBorD therapy; however, during her course of therapy, cyclophosphamide was withheld due to toxicity, and she continued dexamethasone and bortezomib treatment. Unfortunately, the patient continued to clinically deteriorate with anasarca, worsening kidney function, and dermatitis/mucositis. She underwent a skin biopsy which was negative for amyloids. A follow-up echocardiography

1 month into therapy showed similar findings as previously, except for worsening tricuspid valve regurgitation. While on treatment, the patient developed worsening respiratory distress and decreased level of consciousness and went into pulseless electrical activity; despite cardiopulmonary resuscitation, the patient passed away.

Clinical learnings. The late presentation of cardiac symptoms and lack of recognition of aortic stenosis as one of the presentations of cardiac amyloidosis, coupled with a rapid decline of the cardiac and renal function contributed to the poor outcome in this patient. Indeed, when the TAVR registry was systematically screened, up to 15% of patients with preserved EF and aortic stenosis were shown to have cardiac amyloidosis.[22]

Although initial therapy resulted in the reduction of FLC, pre-existing advanced myocardial and renal damage lagged in response. Earlier utilization of daratumumab may have alleviated the profound tissue and organ toxicity from the high levels of circulating FLC and its high tissue affinity. The thyroid symptoms and dysfunction were suspected to be related to amyloid depositions in the thyroid which further highlights the severe multi-organ toxicity caused by the rapid increase of FLCs. Of note, the abdominal fat pad biopsy was amyloid positive while the skin biopsy was negative in this patient highlighting the variability that can occur among non-cardiac tissue biopsies.

Finally, this case highlights that equivocal scintigraphy can be associated with AL amyloidosis (~10% of patients) and not only early-stage TTR, and therefore should always be preceded by assessment for FLC with serum and urine immunofixation to ensure accurate interpretation.[43] Cardiologists commonly conduct cardiac scintigraphy simultaneously to the assessment for the presence of monoclonal protein, as is recommended in the 2023 American College of Cardiology guidelines.[43] When patients present to cardiology departments, it is important not to miss or delay this step of hematological assessment to ensure accurate and rapid diagnosis of AL amyloidosis.

Collective learnings and implications for clinical care

The range of case studies presented in this series allows some key learnings and themes to be drawn and elaborated (Box 1). First, early recognition of the disease can radically improve prognosis, and several key signs should point to cardiac amyloidosis. A differential diagnosis of cardiac amyloid should immediately come to mind if a patient presents with cardiac symptoms, particularly if they are in a hypercoagulable state with evidence of systemic embolization, congestive HF, or aortic stenosis with renal impairment, alongside an echocardiogram showing a thick LV with discordant or low ECG voltage. In such cases, urgently obtaining FLC and immunofixation will expedite an early diagnosis. In some of the presented cases, amyloidosis could have been suspected earlier and may have led to improved patient outcomes. Accurate tissue typing in amyloidosis is essential to provide appropriate therapy for patients, but the technology is not readily available worldwide. To facilitate greater collaboration and ensure available technologies can be accessed by more institutions, an international hub and spoke network is being developed by ISA.[44]

Box 1. Key learnings in the management of AL amyloidosis.

- **Time is of the essence:** the direct toxicity of the amyloid light chain results in a rapidly progressing disease that warrants swift diagnosis and treatment (within 1 week) to improve patient prognosis
- Maintaining a high degree of **clinical suspicion** is crucial for diagnosis given the myriad symptoms and variable presentations
- **Enhanced multidisciplinary collaboration is essential**, particularly between cardiologists (given cardiac involvement is found in at least 50% of cases) and hematologists to ensure rapid diagnosis and treatment, ideally within 1 week
- **AL is a hematologic emergency:** in stark contrast with MM, which is a slow, indolent disease, AL is a rapidly progressing fatal cardiac 'attack'
- Even at low concentrations, amyloidogenic light chains are capable of **rapid deposition** leading to irreversible cardiac damage
- **Dara-CyBorD** is the preferred **first-line therapy** and early initiation may eliminate the need for ASCT. Conversely, delaying treatment can result in advanced myocardial toxicity that results in a prohibitively high risk for ASCT

ASCT, autologous stem cell transplant; AL, amyloid light chain; Dara-CyBorD, daratumumab-cyclophosphamide-bortezomib-dexamethasone; MM, multiple myeloma.

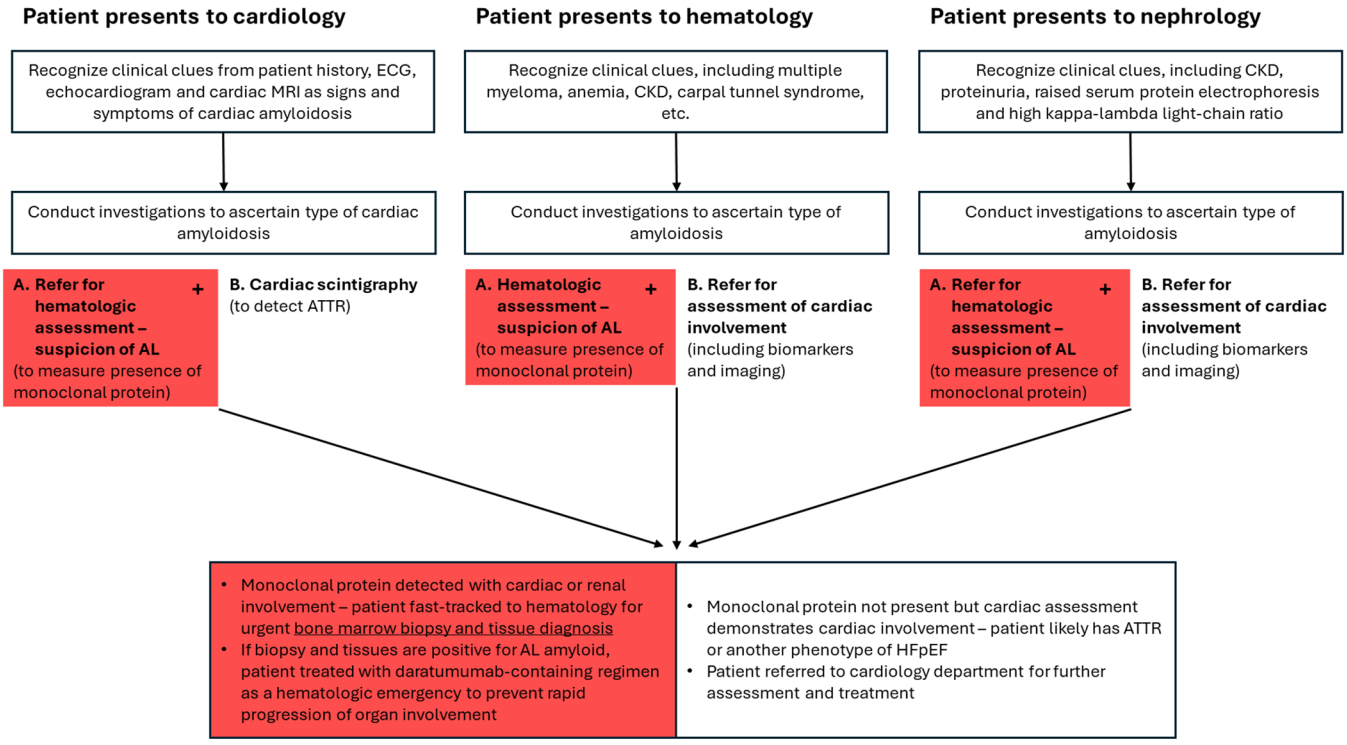

Figure 1. Proposed pathway for patient diagnosis, treatment, and referral for AL amyloidosis.
AL, amyloid light chain; ATTR, transthyretin amyloidosis; CKD, chronic kidney disease; ECG, electrocardiogram; HFpEF, heart failure with partial ejection fraction; MRI, magnetic resonance imaging.

A second important learning is that multidisciplinary collaboration is essential (Figure 1). From the cardiologist's perspective, this means early involvement of hematologists is crucial. The collaboration should be focused on overcoming logistical barriers to obtaining and confirming a histopathological diagnosis within a week to enable rapid diagnosis and treatment. Given cardiologists will commonly conduct PYP scintigraphy when cardiac amyloidosis is suspected, it is important to ensure these results are interpreted in the context of hematological assessment for the presence of monoclonal protein—these tests should be conducted simultaneously for rapid diagnosis.[43] Notably, PYP scintigraphy may be grade 1 or equivocal in patients with AL amyloidosis, and even more rarely, the co-existence of TTR and AL has been reported. In these cases, a tissue biopsy will be essential to determine diagnosis and ensure treatment of AL amyloidosis. Chemotherapy along with targeted treatment such as daratumumab should be initiated as soon as possible to arrest cardiac and renal progression, particularly since the presence of overt HF and elevated cardiac biomarkers is already a very poor prognostic sign. Once the myocardium is affected by direct cytotoxicity of FLCs, indicated by highly elevated cardiac troponin levels,[29] progressive myocardial necrosis is often irreversible. Hematologists need to recognize the pairing of MM with cardiac involvement should trigger the suspicion of AL amyloidosis and provoke rapid investigation, as was the case in some of the presented patients.

The cases highlight the importance of early versus late treatment, dara-CyBorD is the preferred first-line therapy for AL amyloidosis on the basis of the ANDROMEDA trial.[40] Dara-CyBorD yields high percentages of hematologic response, with 78% of patients having a very good partial response or better, and 50%–55% having an organ response 18 months after treatment.[40] This deep remission has profound effects on organ preservation and early initiation of targeted therapy may ultimately eliminate the need for ASCT.[40] Conversely, delaying treatment can result in advanced myocardial

toxicity that results in a prohibitively high risk for ASCT.[19,34]

The risk of thrombosis in HF patients is considerable, and in our patient case series, we document a patient who failed conventional therapy. Patients with AL amyloidosis have an intensely aggressive hypercoagulable state, and the patient who presented failed conventional therapy even though she was in normal sinus rhythm. In the absence of strong data to support the use of direct oral anticoagulants in AL amyloidosis, the standard choice of anticoagulant is either warfarin or low-molecular-weight heparin. This complicates management as warfarin is subject to many drug–drug interactions, which is particularly challenging during chemotherapy, and adequate control of the international normalized ratio can become extremely difficult. A further challenge is that due to the restrictive amyloid cardiomyopathy, patients do not tolerate conventional HF medical therapy well and do poorly on beta-blockers. However, the use of diuretics, mineralocorticoid antagonists, and sodium-glucose cotransporter-2 inhibitors can be used effectively.

AL amyloidosis is a rapidly progressing disease where the circulating FLCs have direct cytotoxic effects that contribute to organ dysfunction. Unlike in MM, while the clonal proliferation in bone marrow may be limited, organ damage is caused by FLCs in circulation. Therefore, traditional criteria of having a plasma cell clone $\geqslant 10\%$ may not be observed on a bone marrow biopsy, yet aggressive cardiac and renal involvement will be evident; pathologists should be attuned to this discordance.

Conclusion and "call to action"

The consensus of the authors, who are experienced in both cardiac amyloidosis as well as the hematological aspects of this disease, is that a core multidisciplinary team is needed to accomplish the difficult task of early recognition, diagnosis, and fast-track access to initiating therapy for AL amyloidosis. Standard-of-care treatment should be more widely available; however, due to the relative rarity of the disease, coupled with insufficient cardiology and hematology expertise outside of specialized centers, this is not always practical. As such, centers with the relevant expertise should take the lead in accepting patients for transfer or fast-track evaluation, as part of their standard procedures or as part of an emergency process. Finally, experts in the field should help to increase awareness and skill sets regarding diagnosis protocols and increase the index of suspicion of AL amyloidosis among their peers.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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Availability of data and materials

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Supplemental material

Supplemental material for this article is available online.

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