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CASE REPORT

Cardiac and renal AL amyloidosis controlled by autologous stem cell transplantation for 17 years accompanying late onset atrial fibrillation and complete atrioventricular block

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Abstract

Amyloid light chain (AL) amyloidosis is a rare hematologic disease that may involve multiple organs. Amongst the organs, cardiac involvement causes the greatest concern as its treatment is challenging. Diastolic dysfunction rapidly progresses to decompensated heart failure, pulseless electrical activity, and atrial standstill due to electro-mechanical dissociation resulting in death. High-dose melphalan plus autologous stem cell transplantation (HDM-ASCT) is the most radical treatment but its risk is very high and thus only less than 20% of patients can receive this therapy under criteria that can suppress treatment-related mortality. In substantial proportion of patients, levels of M protein remain elevated, and organ response cannot be achieved. Moreover, relapse may occur, making prediction of treatment response and judgement of disease eradication very difficult. Herein we report a case of AL amyloidosis who was treated with HDM-ASCT, resulting in preserved cardiac function and resolution of proteinuria for more than 17 years after HDM-ASCT ensuing atrial fibrillation and complete atrioventricular block required management by catheter ablation and pacemaker implantation 10 years and 12 years after transplantation, respectively.

Keywords AL amyloidosis · Autologous stem cell transplantation · Renal amyloidosis · Cardiac amyloidosis

Introduction

Amyloid light chain (AL) amyloidosis may involve multiple organ systems including renal, cardiac, gastrointestinal, nervous, hepatic, and pulmonary systems. Additionally, its manifestations may overlap with common diseases making adequate diagnosis suspicion difficult. However, the commonest presentations are renal (nephrotic syndrome, renal insufficiency) and cardiac (shortness of breath, syncope) disease and they occur in 48–80% and in 21–70%, respectively. When combined with liver disease (isolated ALP elevation), polyneuropathy (paresthesia, numbness, muscle weakness, orthostatic hypotension, erectile dysfunction, oral and eye desiccation), and gastrointestinal disease (weight loss, diarrhea, bleeding), 68% of cases involve more than one organ systems, which becomes a clue to suspect AL amyloidosis [1]. Sudden death by pulseless electrical activity, ventricular fibrillation, and pulmonary embolism are important causes of death and makes up one-third of death within 90 days after diagnosis [2]. Compared with other heart diseases, pulseless electrical activity is more common in AL amyloidosis; thus, some patients have a higher risk of sudden death that cannot be prevented by an implanted cardioverter defibrillator [2]. Additionally, a first-degree atrioventricular block may potentially lead to a complete atrioventricular

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block [3]. Overall, cardiac disease is the most common (63.6%) cause of death in patients with AL amyloidosis [4].

Amyloidogenic point mutation due to somatic hypermutation in antibody-producing cells is considered as an etiologic factor of amyloid fibril formation [5]. AL amyloidosis can be diagnosed with Congo-red staining and with typing by kappa or lambda light chain stain after a biopsy of the involved organ. As results of serum and urine immune-electrophoresis are often negative, and the free light chain kappa/lambda ratio is normal in more than 20% of all cases [6] and a combination of these tests even fails to detect in some cases, histologically diagnosing AL amyloidosis is important.

Treatment usually consists of chemotherapeutic agents against pathological plasma/B cells. Currently, melphalan and dexamethasone (MD) therapy [7], BMDex therapy, wherein bortezomib is added to MD [8], CyBorD therapy (bortezomib, cyclophosphamide, and dexamethasone) [9], high dose melphalan plus autologous stem cell transplantation HDM-ASCT [7], and daratumumab ± CyBorD therapy [10] are used to treat AL amyloidosis. Even if a complete hematological response is achieved, patients with minimal residual disease resulted in significantly more frequent progression of organ dysfunction [11] than those without it. Thus, even small amounts of M protein can affect the prognosis of patients, making both the prediction of treatment response and treatment of this disease difficult.

Herein, we report a case of a patient with lambda-type AL amyloidosis who underwent endomyocardial biopsy to rule out hypertrophic cardiomyopathy and was treated with HDM-ASCT, resulting in a favorable outcome.

Case report

A 31-year-old man consulted a primary physician due to dyspnea on exertion and dizziness three months before the first admission. He was diagnosed with bronchial asthma and was prescribed pranlukast hydrate; however, his symptoms did not improve. Two months later he lost consciousness while climbing the stairs, prompting a visit to former institution. On electrocardiography, leads I, aVL, V5, and V6 showed negative T waves. Left ventricular hypertrophy, sinus tachycardia, and reduced ejection fraction (47%) were also noted; hence, bisoprolol fumarate was prescribed. However, coughing when in a supine position was noted, and leg edema developed. He was then admitted to the hospital wherein furosemide was administered for volume control, resulting in the resolution of leg edema and dyspnea on exertion. As he wished to be in a hospital near his residence, he was transferred to our institution.

On admission, his blood pressure was 110/58 mmHg, pulse rate was 110/min, body temperature was 37.1 °C, and body weight was 55.5 kg. Leg edema and dyspnea were not noted. Laboratory data on admission are shown in Table 1. Notable, there was moderate proteinuria (0.97 g/day), and the brain natriuretic peptide (BNP) level was elevated. Additionally, the serum creatinine level was 0.8 mg/dL, eGFR was 92.4 mL/min/1.73 m^2, and urinalysis revealed < 1 red blood cell/high-power field. Gadolinium-enhanced cardiac magnetic resonance imaging revealed asymmetric septal hypertrophy (septum, 16 mm; lateral wall, 10 mm) without late gadolinium enhancement. Thus, hypertrophic cardiomyopathy was initially considered. Left and right ventricular catheterization study and endomyocardial biopsy were undertaken. The coronary angiography result was normal, but pulmonary hypertension and left ventricular end-diastolic pressure (LVEDP) elevation without right ventricular end-diastolic pressure elevation were noted (pulmonary artery pressure, 56/33 mmHg; LVEDP, 38 mmHg). Considering heart failure due to diastolic dysfunction, bisoprolol fumarate was switched to carvedilol 1.25 mg, and serum alpha-galactosidase activity was measured to rule out cardiac Fabry disease (71.6 nmol/pg/h; reference range, 37.6–230.1).

Biopsy results revealed amorphous amyloid deposition between cardiomyocytes, and Congo red staining revealed granular deposition of amyloid (Fig. 1A), which immunohistochemistry revealed to be lambda-type. Electron microscopy also revealed fibrils measuring 7–8 nm in diameter. Kidney biopsy was also performed to determine the etiology of proteinuria. Light microscopic examination showed global sclerosis in 2 out of 36 glomeruli. Most of the preserved glomeruli showed no abnormalities; however, small areas of the mesangium, interlobular arteries, and arterioles showed amorphous material deposition with apple-green birefringence under polarizing light that were positive for Congo red staining (Fig. 1B). Immunofluorescence was negative for immunoglobulins (IgG, IgA, and IgM) and complement components (C3, C4, and C1q). Additionally, the affected areas were positive for lambda (Fig. 1C) but negative for kappa, amyloid A, beta-2 microglobulin, and transthyretin. Electron microscopy showed randomly arranged fibrils in the mesangial region measuring 7–12 nm in diameter (Fig. 1D); however, foot process effacement was not observed. The patient was diagnosed with AL amyloidosis, and additional examinations, including flow cytometry of bone marrow aspirate (normocellular bone marrow with a mild increase of plasma cell (6.6%) and cytoplasmic lambda positivity in CD38 positive cells, indicating clonal proliferation), PYP scintigraphy (no PYP accumulation), karyotyping (46, XY normal karyotype), gastrointestinal and colonic fiberscopy (amyloid deposition in the wall of arterioles in the submucosa of erosive Bauhin's valve), cutaneous biopsy (no amyloid deposition), and abdominal ultrasonography (no hepatomegaly) were undertaken to determine the extent of disease.

Table 1 Blood laboratory tests and urinalysis results on admission are shown

TP	7.1	g/dl	RBC	5.13	×10^6/uL	IgG	718	mg/dl	Protein electrophoresis		
Alb	4.1	g/dl	Hb	14.2	g/dl	IgA	82.9	mg/dl	Alb	65.6	%
T-bil	1.4	mg/dl	Hct	43.8	%	IgM	47.2	mg/dl	α1	4.4	%
UN	16	mg/dl	MCV	85.4	fL	IgE	10	U/ml	α2	10.2	%
Creatinine	0.8	mg/dl	MCH	27.7	pg	CH50	37	U	β	9.6	%
Uric acid	7.1	mg/dl	MCHC	32.4	%	C3	92	mg/dl	γ	10.2	%
T-chol	225	mg/dl	Ret	4.3	×10^4/μL	C4	19	mg/dl			
Na	143	mEq/L	Plt	341	×10^3/uL						
K	4.9	mEq/L	WBC	5.4	×10^3/uL	F-T4	1.38	ng/dl			
Cl	103	mEq/L	Nseg	59.1	%	F-T3	378	pg/dl			
Ca	5.0	mEq/L	Eos	3.4	%	TSH	2.093	μU/ml	Uvolume	1198	mL
P	3.6	mg/dl	Bas	1.3	%				UP	81	mg/dl
AST	26	IU/L	Mono	6.3	%	FPG	86	mg/dl	UN	493	mg/dl
ALT	31	IU/L	Lym	29.9	%	HbA1c	5.1	%	Cr	97	mg/dl
LD	169	IU/L	APTT	23.1	s				Na	86	mEq
ALP	191	IU/L	PT	12.7	s	pH	7.44		K	17	mEq
GGT	75	IU/L	PT-INR	1.04		pCO2	39	mmHg	Cl	84	mEq
Amy	69	IU/L	Fe	63	μg/dL	pO2	101	mmHg	β2MG	52	μg/L
CK	51	IU/L	UIBC	349	μg/dL	HCO3	26	mEq/L	Osm	424	mOsm/kg
CRP	0.1	mg/dl	Ferritin	55	ng/mL	BE	2.2	mEq/L	UIgG	1.3	mg/dl
			ACE	17.0	IU/L				UIgA	< 0.3	mg/dl
			HBsAg	–		BNP	564.0	pg/mL	UIgM	< 0.3	mg/dl
			HCV-Ab	–					Ualb	> 250	mg/dl
			RPR	–							

Based on the results of the examinations, systemic amyloidosis was noted and involved the heart, kidneys, and gastrointestinal tract. After acknowledgment by the institutional ethical committee, we obtained written informed consent from the patient to perform autologous stem cell transplantation (ASCT) after conditioning with vincristine, adriamycin, and doxorubicin (VAD-ASCT). Two months after admission, VAD chemotherapy was instituted (vincristine 0.4 mg/day, adriamycin 14.5 mg/day, and dexamethasone 40 mg/day for four consecutive days, then doxorubicin 40 mg twice in two weeks). One month after induction, the second course of VAD was administered, and peripheral stem cell harvest was planned; however, the patient developed fever due to a respiratory infection, which was treated with sulbactam–ampicillin. Meanwhile, a beta-D glucan level > 600 pg/mL and opacity in the upper fields of both lungs raised suspicion of *Pneumocysfis carinii* pneumonia; he was then treated with sulfamethoxazole-trimethoprim. Methylprednisolone, fosfluconazole, and carperitide were also administered. The patient's condition improved and he was discharged two months later.

Seven months after the first admission, the patient was administered figrastim 500 μg/day for three consecutive days. Meanwhile, 2.56×10^6/kg CD34 + cells were harvested in two consecutive days. After readmission the next month, L-PAM 110 mg (70 mg/m^2/day) was administered for two consecutive days after prophylactic administration of acyclovir, fluconazole, and tosfloxacin. The next day, peripheral blood stem cell transplantation was performed. On day 4 he experienced diarrhea, which was considered as regimen-related toxicity. On day 6, ceftazidime 3 g/day was initiated for febrile neutropenia. On day 8, his serum creatinine level reached 1.5 mg/dL; therefore, extracellular fluids were administered. On day 10, eruptions were observed on his trunk and extremities; hence, ceftazidime was switched to meropenem. On day 11, engraftment was achieved; however, his urine output decreased, while his body weight and cardio-thoracic ratio increased. Additionally, his serum creatinine level reached 2.9 mg/dL; therefore, dobutamine 3 mg/kg/h, dopamine 3 mg/kg/h, and furosemide continuous infusion were initiated. On day 14, his fever lysed, his urine output increased, and his serum creatinine level improved to 0.8 mg/dL, suggesting that the etiology of acute kidney injury was prerenal. On day 18, dobutamine and dopamine were discontinued, and on day 20, he was discharged.

Response to treatment is shown in Fig. 2. Urinary protein improved from 0.83 g/gCr to 0.02 g/gCr half a year after ASCT; however, transient nephrotic range proteinuria was noted (4.62 g/gCr and 2.96 g/gCr, two months after VAD and three months after ASCT, respectively), which improved

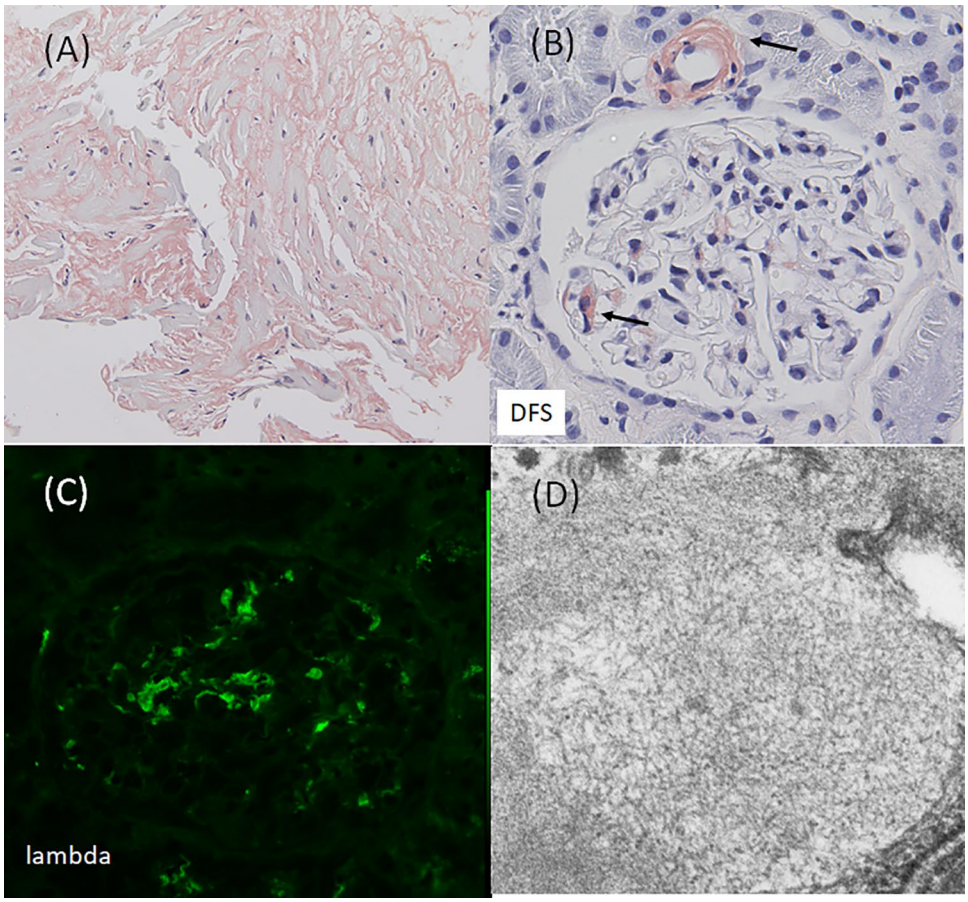

Fig. 1 **A** Congo red staining of endomyocardial biopsy specimen showing amyloid deposition in the interstitial tissue of cardiomyocytes. **B** DFS stain of renal biopsy specimen showing slight amorphous material deposition in the mesangial area and arterioles. **C** Immunofluorescence stain of renal biopsy specimen by lambda light chain showing mesangial deposition. **D** Electron microscopy showing mesangial amyloid deposition

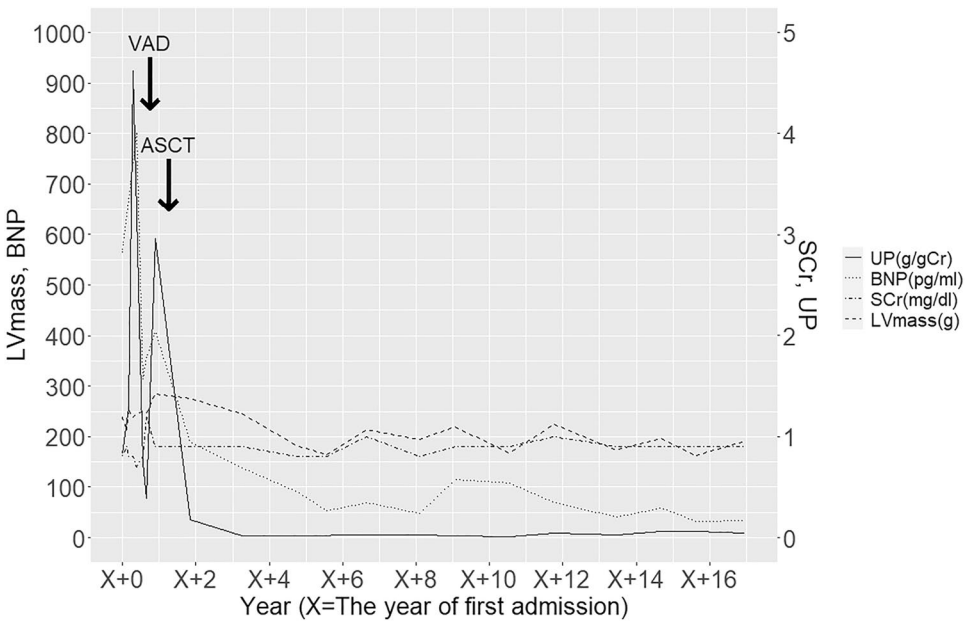

Fig. 2 Time course of urinary protein (UP, right axis, solid line), brain natriuretic peptide (BNP, left axis, dashed line), serum creatinine (SCr, right axis, dot-dash line), and left ventricular mass (LV mass, left axis, dotted line) are shown. The timing of VAD induction and ASCT therapy are also shown

to within normal range thereafter. The serum creatinine level was maintained within the normal range for 18 years after diagnosis, and urinary protein completely disappeared. The estimated left ventricular mass improved with a sustained decrease in levels of BNP. Additionally, the left atrial

diameter also improved (from 45 mm pretransplant to 37.1 mm 16 years after transplantation).

Eleven years after the first admission, paroxysmal atrial fibrillation was detected by a routine outpatient electrocardiogram. Although his heart rate was less than 100 beats/min and the CHADS2 score was 0, anticoagulation therapy with apixaban 10 mg was initiated. The next month, pharmacological defibrillation with pilsicainide was attempted but failed. Two months later, direct current cardioversion was performed, and his heart rhythm returned to sinus. Apixaban was discontinued 6 months later.

Thirteen years after the first admission, he felt his pulse as being slow, prompting a visit to the emergency department. Complete atrioventricular block was detected, prompting admission and permanent pacemaker implantation. The next month, frequent episodes of atrial fibrillation prompted the re-initiation of apixaban. The following year, catheter ablation for atrial fibrillation was performed. Subsequently, the pacing ratio gradually increased, and atrial fibrillation resolved. During this time, the left atrial diameter was approximately 40 mm, which was unchanged before and after the onset of atrial fibrillation and complete atrioventricular block, and M protein remained negative. Currently, he has maintained on carvedilol 10 mg with tri-monthly follow-ups as an outpatient.

Discussion

We presented a case of AL amyloidosis case with congestive heart failure and proteinuria of over 1 g/day that resolved after HDM-ASCT and VAD induction therapy. Following treatment, left ventricular hypertrophy resolved, and proteinuria improved. Alpha-galactosidase activity was measured to exclude Fabry disease, as it also presents with heart failure and proteinuria and is an important differential diagnosis. Hypertrophic cardiomyopathy was also a differential diagnosis as it occurs in the thirties in 7.1% of all cases [12]. As the serum and urine immune-electrophoresis and late gadolinium enhancement results were negative, cardiac biopsy were required to confirm cardiac involvement.

Reduced ejection fraction, diastolic dysfunction, and arrythmia were noted in our case due to cardiac lesions caused by AL amyloidosis. Atrial fibrillation, atrial flutter, (complete) atrioventricular block, and pulseless electrical activity, may occur in AL amyloidosis; however, these are considered electro-mechanical dissociation, and reports on atrial standstill and atrial thrombus formation even with present P waves on electrocardiograms [13] and failure to improve survival rates by ICD implantation [14] support this notion.

Based on the absence of diabetes, hypertension, and obesity, improvement in the left atrial diameter after treatment, and good treatment response to catheter ablation, AL amyloidosis-related atrial fibrillation and age-related atrial fibrillation were considered. As catheter ablation for AL amyloidosis-related atrial fibrillation has a three-year relapse-free survival rate of 60% [15], it may be considered as a late treatment option if hematological response is favorable, as was in our case. Notably, cardioversion fails to maintain sinus rhythm in 80% of cases in one year [16].

Kidney biopsy revealed mesangial deposition of amyloid, which might have been related to proteinuria in this case and as indicated by Hoelbeek et al. [17]. It is unclear why transient worsening of proteinuria was seen after VAD chemotherapy and ASCT; however, a favorable response to treatment indicated no progression of renal amyloidosis even if no repeat biopsy was undertaken. In our case, pacemaker implantation was required for a complete atrioventricular block 12 years after HDM-ASCT. Although we did not perform repeat bone marrow aspiration and flow cytometry and it was unclear whether residual amyloid-producing clones remained, these procedures may be considered for future cases due to the introduction of potent agents such as daratumumab or bortezomib, which can be added to HDM-ASCT. Although HDM-ASCT has become safer over the past two decades with suppressed treatment-related mortality [18], it is still considered as a high-risk procedure and new safer agents were introduced albeit with undetermined long-term efficacy. Therefore, it is important to individualize treatment so that young patients like our case can receive sufficient strength regimen, desirably in advance of the onset of a remote complication.

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Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Informed consent The patient gave us his informed consent on HDM-ASCT. The study conforms to the Declaration of Helsinki.

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