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CASE REPORT

A case of light chain (AL) amyloidosis with heart failure, renal dysfunction, and heparin-induced thrombocytopenia successfully treated with peritoneal dialysis

Shingo Nakayama[1] · Satoshi Kinugasa[1] · Takuo Hirose[1,3] · Yuka Miyake[1,2] · Kohei Ota[4] · Maya Onzo-Toyama[1,2] · Ikuko Oba-Yabana[1] · Hannah Nakamura[1] · Junichi Tani[1] · Wako Yumura[1,5] · Takefumi Mori[1,3]

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Abstract

A 65-year-old woman was hospitalized for heart failure and pneumonia in a nearby hospital. She had been previously diagnosed as light chain (AL) amyloidosis and treated with melphalan plus dexamethasone (Mel-Dex), and lenalidomide plus dexamethasone (Len-Dex). She started treatment including antimicrobials and diuretics, but her renal function worsened progressively, and she was transferred to our hospital for nephrological care. She was treated with antimicrobials, noradrenaline, dobutamine, and continuous hemodiafiltration. Her general condition gradually stabilized, and she was switched to intermittent hemodialysis (HD). However, HD was discontinued due to intradialytic hypotension and the development of heparin-induced thrombocytopenia. Her renal replacement therapy was switched to peritoneal dialysis (PD), which enabled good volume control and stable cardiac function. She was discharged and is still in good condition, without serious complications and achieving a considerably better prognosis than was predicted. Our case suggests that PD is an effective modality for patients with AL amyloidosis with heart failure and renal dysfunction.

Keywords AL amyloidosis · Peritoneal dialysis · Heparin-induced thrombocytopenia · Intradialytic hypotension

Introduction

Light chain (AL) amyloidosis is characterized by the aggregation of misfolded immunoglobulin light chains in various organs such as the heart, the kidney, the liver, and the neural system, causing organ failure [1, 2]. Cardiac involvement is the leading cause of morbidity and mortality in amyloidosis. The heart is affected in approximately 50% of patients with AL amyloidosis, and congestive heart failure is the presenting clinical manifestation in approximately one-half of these patients [3, 4]. Patients with severe cardiac involvement are known to have the worst prognosis [5]. When patients with cardiac AL amyloidosis are untreated, the median survival is 6 months from the onset of heart failure [6]. In addition, the poor outcome with AL amyloidosis patients undergoing dialysis is reported in several studies [7, 8]. Bollee et al. reported that mortality was higher in AL amyloidosis than in amyloid A (AA) amyloidosis cases who received dialysis, and AL patients without cardiac amyloidosis had more than a two-fold longer median survival than those with heart involvement [8]. There are only a few studies showing the long-term efficacy of peritoneal dialysis (PD) in AL amyloidosis patients. We report a case of AL amyloidosis with heart failure and renal dysfunction that was treated with PD, which led to the achievement of long-term survival.

✉ Satoshi Kinugasa
kinugas-tky@umin.ac.jp

1 Division of Nephrology and Endocrinology, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, 1-15-1 Fukumuro, Miyagino-ku, Sendai, Miyagi 983-8536, Japan

2 Department of Nephrology, Japan Self-Defense Forces Sendai Hospital, Sendai, Japan

3 Division of Integrative Renal Replacement Therapy, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan

4 Department of Nephrology and Endocrinology, National Defense Medical College, Tokorozawa, Japan

5 Department of Nephrology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

Case report

A 65-year-old Japanese woman who presented with dyspnea visited a nearby hospital and was hospitalized for heart failure and pneumonia in October 2017. Urine immunoelectrophoresis revealed the presence of Bence Jones protein type λ. Direct fast scarlet staining showed amyloid deposition in the muscularis mucosa, and in the vessel walls of the submucosa in the rectum. Thus, she was diagnosed as AL amyloidosis when she was 58-years-old. She was treated with melphalan plus dexamethasone (Mel-Dex), and subsequently with lenalidomide plus dexamethasone (Len-Dex). Echocardiography before admission revealed the following findings: left ventricular end-diastolic diameter, 45.1 mm; left ventricular end-systolic diameter, 31.4 mm; ejection fraction, 57.9%; interventricular septal thickness, 12.9 mm; left ventricular posterior wall thickness, 12.7 mm; E/A ratio, 2.16; deceleration time, 169 ms; and E/e' 23.6. Extensive thickening of the left ventricle and the interventricular septum, and diastolic dysfunction (restrictive pattern) were observed, and these abnormalities were consistent with cardiac amyloidosis. After admission, she started treatment including antimicrobials and diuretics. Her renal function gradually deteriorated, and serum creatinine levels (sCr) rose to 2.0 mg/dL. She developed respiratory failure in spite of the treatment and required tracheal intubation. Her respiratory condition improved after changing the antimicrobials and adjusting the dose of diuretics, and she was successfully extubated. However, since her renal function worsened rapidly and her sCr reached 10.77 mg/dL, she was transferred to our hospital for nephrological care including renal replacement therapy (RRT). On admission to our hospital, her height was 151.0 cm, and her body weight was 53.8 kg. Her body temperature was 37.1 ℃, her blood pressure was 108/68 mmHg, and her heart rate was 105 beats/minute with a regular rhythm. Physical examination revealed coarse crackles of the bilateral lower lung fields and pitting edema of her lower extremities. Arterial blood gas analysis on 7 L of O_2 via OxyMask™ indicated a pH of 7.342, PaO_2 77.9 Torr, $PaCO_2$ 25.7 Torr, and HCO_3^- 13.6 mmol/L. Other clinical laboratory data, which are summarized in Table 1, are as follows: white blood cell count, 6.8×10^3/μL with 77.7% neutrophils; hemoglobin level, 10.3 g/dL; platelet count, 19.5×10^4/μL; sCr, 11.42 mg/dL; estimated glomerular filtration rate [9], 3.0 mL/min/1.73 m^2; blood urea nitrogen, 117 mg/dL; total protein without M-protein, 5.6 g/dL; albumin, 2.2 g/dL; C-reactive protein, 2.24 mg/dL; kappa free light chain (FLC), 130.0 mg/L; lambda FLC, 193.0 mg/L; FLC ratio, 0.67; brain natriuretic peptide (BNP), 441.5 pg/mL; N-terminal pro-B-type natriuretic peptide (NT-proBNP), 37,377.0 pg/mL; troponin T (cTnT), 0.152 ng/mL; immunoglobulin G, 1325 mg/dL; immunoglobulin A, 712 mg/dL; and immunoglobulin M, 46 mg/dL. Serum complement factors 3 and 4, and complement hemolytic activity were normal. Antinuclear antibodies, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies were negative. Her urinalysis revealed proteinuria of 1.29 g/gram urinary creatinine and < 1 red blood cell/high-power field. Computed tomography showed bilateral pleural effusions and infiltrating lesions indicating pneumonia in both lungs (Fig. 1). Echocardiography after admission showed the following findings: left ventricular end-diastolic diameter, 41.8 mm; left ventricular end-systolic diameter, 28.7 mm; ejection fraction, 59.6%; interventricular septal thickness, 14.8 mm; left ventricular posterior wall thickness, 14.5 mm; E/A ratio, 1.14; and E/e' 14.75. Extensive thickening of the left ventricle and the interventricular septum, and diastolic dysfunction were observed, and thus she was diagnosed as heart failure with preserved ejection fraction (HFpEF). She was classified as class IV of the New York Heart Association functional classification, and group C (Wet-Cold) of the Nohria-Stevenson classification. She was also diagnosed with advanced cardiac amyloidosis after cardiologic consultation (Fig. 2). We started treatment with antimicrobials, noradrenaline, dobutamine, and continuous hemodiafiltration (CHDF) (Fig. 3). The settings of CHDF were as follows: blood flow rate 60–80 mL/min, dialysate flow rate 100–300 mL/h, and filtration rate 100–300 mL/h. Her general condition gradually stabilized, and she was switched to intermittent hemodialysis (HD). HD was performed for 4 h with a blood flow rate of 100–120 mL/min, using a polyethersulfone dialyzer (PES-15Eαeco, Nipro Corporation, Osaka, Japan). However, she developed thrombocytopenia, and anti-heparin–platelet factor 4 (PF4) antibodies became positive (1.1 U/mL; negative value was below 0.9 U/mL) on the 14th day after admission. We discontinued heparin due to suspected heparin-induced thrombocytopenia (HIT), and administered a heparin-free dialysis regimen and argatroban. In addition, she had intradialytic hypotension (IDH). Under these circumstances, it was difficult to continue HD, and thus we switched the RRT to PD. A PD catheter was inserted under local anesthesia on the 16th day after admission. From the 2nd postoperative day, continuous ambulatory PD was initiated, and we adjusted the PD regimen based on the patient's volume status. The PD regimen was finally fixed to automated peritoneal dialysis utilizing 4 L of neutralized buffered 1.35% glucose peritoneal dialysate (Midpeliq 135L, Terumo Corporation, Tokyo, Japan) and a final dwell of 1 L 7.5% icodextrin peritoneal dialysis solution (Nicopeliq, Terumo Corporation, Tokyo, Japan) per day. The fluid removal by PD was approximately 500 mL/day, and we were able to

Table 1 Laboratory data on admission

Urinalysis		Uric acid	10.4 mg/dL
Protein	(+)	Sodium	136 mEq/L
Occult blood	(−)	Potassium	4.2 mEq/L
Red blood cell	< 1/HPF	Chloride	105 mEq/L
Protein content	1.29 g/gCr	Calcium	8.8 mg/dL
Bence-Jones protein	(−)	Phosphorus	6.7 mg/dL
β2-MG	8.3 IU/L	Iron	43 μg/dL
NAG	207 μg/L	Ferritin	462 ng/mL
Complete blood cell count		CRP	2.24 mg/dL
White blood cells	6800/μL	IgG	1325 mg/dL
Neutrophil	77.7%	IgA	712 mg/dL
Hemoglobin	10.3 g/dL	IgM	46 mg/dL
Hematocrit	31.1%	C3	69 mg/dL
Platelets	19.5×10^4/μL	C4	18 mg/dL
Biochemistry/immunology		CH50	45.3 U/mL
Total protein	5.6 g/dL	RF	< 5 IU/mL
Albumin	2.2 g/dL	Antinuclear antibody	< 40
Total bilirubin	0.4 mg/dL	MPO-ANCA	< 1.0 U/mL
AST	16 U/L	PR3-ANCA	< 1.0 U/mL
ALT	13 U/L	Anti-GBM antibody	< 2.0 U/mL
ALP	215 U/L	Cryoglobulin	(−)
LDH	279 U/L	IEP	(−)
γ-GTP	51 U/L	FLC κ/λ ratio	0.67
Amylase	78 U/L	HBs antigen	(−)
CK	37 U/L	HCV antibody	(−)
Glucose	96 mg/dL	BNP	441.5 pg/mL
Blood urea nitrogen	117 mg/dL	NT-proBNP	37,377.0 pg/mL
Creatinine	11.4 mg/dL	Troponin T	0.152 ng/mL
eGFR	3.0 mL/min/1.73 m^2		

β2-MG beta 2-microglobulin, *NAG* N-acetyl-beta-D-glucosaminidase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *LDH* lactate dehydrogenase, *γ-GTP* gamma-glutamyl transpeptidase, *CK* creatine kinase, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *IgM* immunoglobulin M, *C3* complement 3, *C4* complement 4, *CH50* complement hemolytic activity, *RF* rheumatoid factor, *MPO-ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibody, *PR3-ANCA* proteinase 3 anti-neutrophil cytoplasmic antibody, *GBM* glomerular basement membrane, *IEP* immunoelectrophoresis, *FLC* free light chain, *HBs* antigen hepatitis B surface antigen, *HCV* hepatitis C virus, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-B-type natriuretic peptide

manage the patient's volume status successfully by this regimen. The urine volume was approximately 1000 mL/day with the administration of furosemide 160 mg/day, spironolactone 50 mg/day, and tolvaptan 15 mg/day and did not change during hospitalization, indicating good residual renal function. She was discharged home on the 44th day after admission. The BNP and NT-proBNP levels had improved to 195.1 pg/mL and 12,922.0 pg/mL at discharge, respectively. Since then, she has been followed up as an outpatient, and she continues PD for 2 years without any serious symptoms or complications. She has a good quality of life and enjoys traveling around Japan (Fig. 3). The results of echocardiography after discharge were as follows: left ventricular end-diastolic diameter, 42.9 mm; left ventricular end-systolic diameter, 31.0 mm; ejection fraction, 54.1%; interventricular septal thickness, 16.4 mm; left ventricular posterior wall thickness, 11.4 mm; E/A ratio, 0.71; and E/e' 8.57. These findings were similar to those during hospitalization although the diastolic dysfunction was slightly improved.

Discussion

We experienced a case of AL amyloidosis with heart failure and renal dysfunction who underwent PD and achieved long-term survival. There are several prognostic models which enable the risk stratification of patients with AL

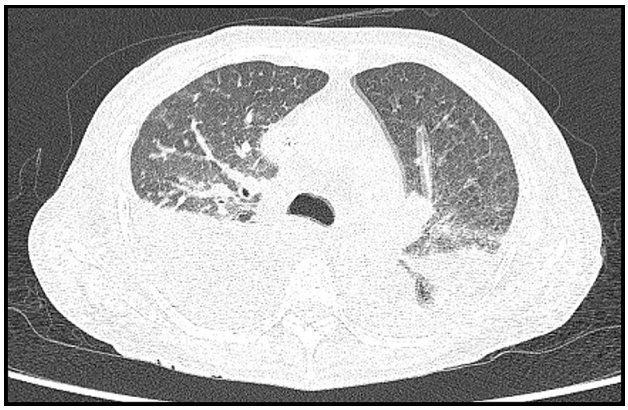

Fig. 1 Computed tomography of the chest showed bilateral pleural effusions and infiltrating lesions indicating pneumonia in both lungs

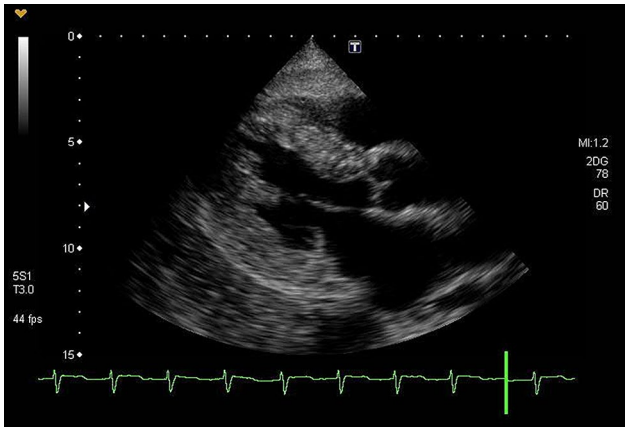

Fig. 2 On transthoracic echocardiogram, the parasternal long axis view demonstrated extensively thickened left ventricular walls, a thickened interventricular septum, and diastolic dysfunction. She was diagnosed as having advanced cardiac amyloidosis after cardiologic consultation

amyloidosis. The Revised Mayo 2012 Stage model is one of the most frequently used models, based on widely available serum biomarkers such as cTnT, NT-proBNP or BNP, and serum immunoglobulin free light chain difference (FLC-diff) [10]. In this model, the median survival times for patients with stages I, II, III, and IV were 94.1, 40.3, 14.0, and 5.8 months, respectively. Meanwhile, the 5-year survival for patients with stages I, II, III, and IV were estimated as 59%, 42%, 20%, and 14%, respectively [10]. The BNP levels had improved to 195.1 pg/mL at discharge. Although renal dysfunction may change the levels of cTnT, NT-proBNP and BNP, and may affect the actual severity of the disease, the present case was classified as stage II, indicating a poor prognosis with the 5-year survival rate of less than 50%. The patient was, however, able to achieve a considerably better prognosis than expected, which we think can be attributed to the utilization of PD. In fact, although she suffered from severe hypotension and required intensive care during hospitalization, now she is free of any serious symptoms or complications and enjoys occasional domestic trips.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are poorly tolerated and tend to cause severe hypotension in patients with cardiac amyloidosis. Therefore, these patients present with refractory heart failure and an extremely poor prognosis [3, 4, 11]. Our case presented with IDH, which is often seen in cardiac amyloidosis patients. PD has been reported to have a smaller effect on hemodynamics than HD, and may be effective in managing the volume status in these patients [12].

The present case was diagnosed as HIT during the patient's clinical course. HIT is one of the common adverse effects of heparin, and HD patients are at risk for HIT because they are repeatedly exposed to heparin used in dialysis circuits. The binding of heparin to PF4 alters its shape and a heparin-PF4 complex is formed. This stimulates the body to produce anti-PF4/heparin antibodies and mediates an immune response, which causes platelet activation and reduction, triggering the thrombotic complications of HIT [13]. Previous reports show that the positivity rate of anti-PF4/heparin antibodies ranges from 5.6% to 12.9% in HD patients [14, 15]. The presence of HIT and IDH made it difficult to choose HD as an RRT.

Previous studies suggest the advantage of PD in patients with amyloidosis. The large area of the peritoneal surface may increase immunoglobulin and light chain removal from the body, preventing amyloid formation, and this mechanism may have improved the prognosis of our case [16]. Furthermore, we previously evaluated the removal of small-, middle-, and large-molecules in a PD model utilizing a neutral pH icodextrin dialysis solution, and we found that larger molecules were removed in a time-dependent manner [17]. We used a neutral icodextrin solution for treatment in the present case, and this might also have led to enhanced amyloid removal. Meanwhile, plasma cell neoplasms including AL amyloidosis are reported to be associated with a risk for arteriovenous fistula thrombosis. Several factors, such as repeated chemotherapy and blood draws, coagulation abnormalities, and amyloid protein deposition in vessels are possible causes of this association [18]. In addition, PD was reported to be beneficial in patients with a high arrhythmic risk, because it facilitated better cardiac electrical stability compared with HD [19]. As many different types of arrhythmia occur in cardiac amyloidosis patients [4, 20], PD may possess the potential to improve the prognosis of these patients.

There was no survival difference between HD and PD in amyloidosis patients in previous studies. However, the few previous studies that exist either have not adjusted the results for cardiac complications or have not assessed

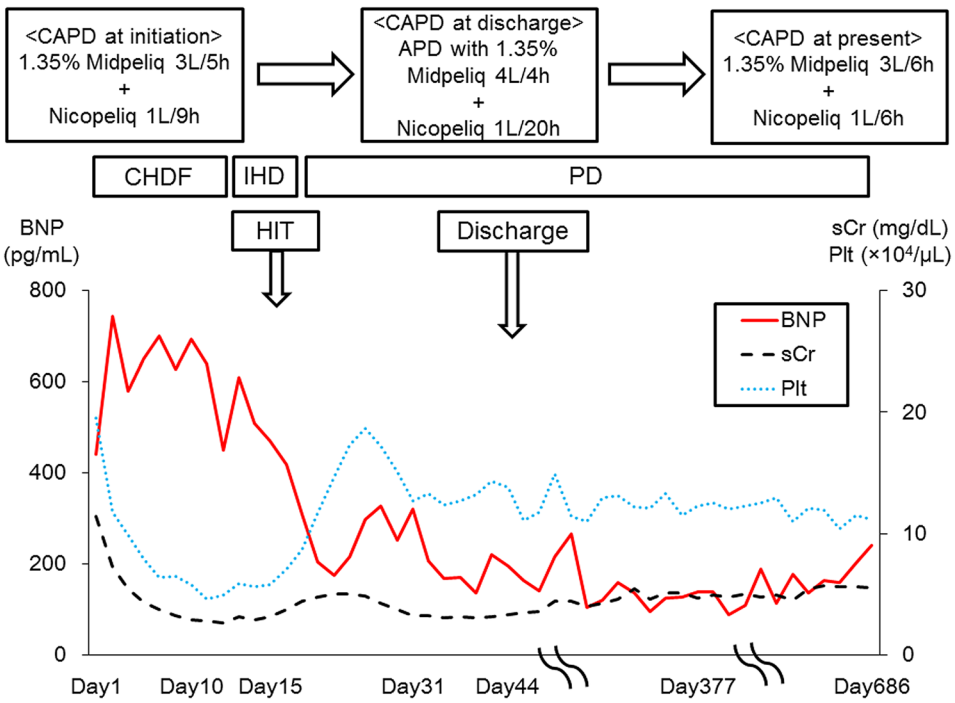

Fig. 3 The clinical course of the treatment of light chain (AL) amyloidosis with severe heart failure and renal dysfunction in a 65-year-old woman. Brain natriuretic peptide (BNP, red solid line), serum creatinine level (sCr, black dashed line), and platelet count (blue dotted line). *CHDF* continuous hemodiafiltration, *IHD* intermittent hemodialysis, *PD* peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis, *APD* automated peritoneal dialysis, *HIT* heparin-induced thrombocytopenia

cardiac involvement at all [7, 21]. Therefore, there is a high possibility that these results are biased, and that actually there is a survival advantage of PD over HD in AL amyloidosis patients. Another study indicated that PD patients could better maintain the various ultrasonographic cardiovascular indices than HD patients [22]. According to a review of the reported case series has shown the benefit of PD in heart failure patients [23]. Furthermore, Courivaud et al. proposed the mechanisms underlying the benefit of PD for heart failure [24], which could also play a beneficial role in patients with amyloidosis. Continuous gentle ultrafiltration with maintained volume and hemodynamic status could have a major benefit in low blood pressure by cardiac amyloidosis. Sodium sieving effect, better control of natremia and restoration of diuretic responsiveness, which is due at least in part to the improvement of renal flow, could have a benefit in amyloidosis with lowered nutritional state and hypoalbuminemia. Lack of impact of neurohormonal status such as the renin-angiotensin system, sympathetic nervous system, and vasopressin, could also have an effective role in suppressing organ damages. In addition to mechanistic benefits, reduced hospitalizations and improve quality of life have large advantages in PD. On the other hand, a previous study reported that mortality risk was higher with PD than HD among incident end-stage renal disease patients with congestive heart failure [25]. Thus, the usefulness of PD is considered to vary depending on the patient background.

In summary, an AL amyloidosis patient with heart failure, renal dysfunction, HIT and IDH was treated with PD, and long-term survival was attained. The present case suggests that PD is an effective modality when AL amyloidosis patients with heart failure, especially HFpEF, have reached end-stage renal disease and require dialysis.

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