Clinical Features of AL Amyloidosis Diagnosed via Renal Biopsy, and Response to Treatment

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Introduction

Primary systemic AL amyloidosis is monoclonal plasma cell dyscrasia characterized by the deposition of light chain proteins and leading to organ dysfunction and death. An estimated annual incidence of AL amyloidosis is 10 per million persons. In Japan, it is reported about 300 cases diagnosed per year. Renal involvement is the most common clinical problem in AL amyloidosis and is present in one -third of patients at diagnosis. The degree of proteinuria depends on the extent of amyloid deposition in the glomeruli, with deposits in the vessels and tubules leading to especially high degrees of proteinuria. Treatments for AL amyloidosis include: melphalan with (MP) or without prednisone; melphalan and dexamethasone; vincristine-doxorubicin-dexamethasone (VAD); thalidomide; and, high-dose melphalan with autologous peripheral blood stem cell transplantation (HDM/SCT).

Median survival is about 13 months from diagnosis without therapy, and 6 months in patients with congestive heart failure at diagnosis.

Subjects and Methods

We identified 8 patients with biopsy-proven AL amyloidosis at Nippon Medical School from January 2006 to December 2009 (6 male and 2 female; age range, 48 to 75 years; mean, 62.8 years). The clinical characteristics of these 8 patients' are listed in **Table 1**. We investigated the clinical features, pathological findings, treatments, renal prognosis, and outcomes.

Results

275 patients including 92 nephrotic syndrome patients were performed renal biopsies at our hospital from January 2006 to December 2009, resulting in diagnosis of AL amyloidosis being 8 patients. All 8 cases fulfilled the clinical diagnostic criteria for nephrotic syndrome. The frequency of AL amyloidosis was 8.7% to nephrotic syndrome patients undergoing renal biopsy, and was 2.9% to all biopsy specimens.

The clinical data at renal biopsy, pathological findings, treatments, and outcomes are shown in **Table 2**. The average of proteinuria level was 7.06 g/day. Renal functions showed slight deterioration and cardiac involvement was suspected in all 8 patients. All had hypotension, and 4 patients had enlargement of the

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Table 1 Characteristics of 8 patients

Case	Age (years)/ Gender (M/F)	Chief complaint	eGFR* (mL/min/1.73 m^2)	Proteinuria (g/day)	Urine volume (mL/day)	Serum Alb (g/dL)
1	75 F	Edema, Proteinuria	64.4	6.9	450	2.6
2	48 M	Edema, Proteinuria	91.5	4.8	800	2.0
3	59 M	Edema, Proteinuria	66.7	9.0	1,100	2.1
4	73 M	Edema, Proteinuria	70.4	7.0	820	2.3
5	67 M	Body weight loss, Proteinuria	46.3	5.4	850	1.8
6	49 F	Edema, Proteinuria	62.5	8.5	2,060	2.1
7	64 M	Edema, Proteinuria	58.7	9.9	1,530	1.3
8	67 M	Edema, Proteinuria	62.3	5.0	850	1.5
Average	62.75		65.35	7.062	1,057.5	1.96

*eGFR: estimated glomerular filtration rate

Table 2 The clinical data at renal biopsy, pathological findings, treatments, and outcomes

Case	immunoelectrophoresis		Main amyloid deposition in the kidney	Plasma cell in bone marrow aspiration	IVST* on echocardiography	treatment	Renal prognosis	outcome
	M-protein	Bence-Jones protein						
1	Negative	BJλ	Small arteries Mesangium > Capillary wall	3%	14 mm	PSL → MP	ECUM	Dead
2	IgGκ	BJκ	Mesangium >> Capillary wall	3.3%	12 mm	DEX	proteinuria decreased	Survive
3	Negative	BJλ	Mesangium >> Capillary wall	1.4%	9 mm	DEX → HDM/SCT	Proteinuria disappeared	Survive
4	IgDλ	BJλ	Interstitium >> Mesangium > Capillary wall	0.6%	10 mm	None	eGFR26.5	Dead
5	Negative	BJ-	Mesangium > Capillary wall (λ light chain)	3%	17 mm	MP	ECUM → HD	Dead
6	Negative	BJλ	Capillary wall	2%	13 mm	DEX → HDM/SCT	Proteinuria disappeared	Survive
7	IgAλ	BJλ	Mesangium area >> Capillary wall	26%	Unknown**	Unknown**	Unknown**	Unknown**
8	Negative	BJκ	Mesangium area > Capillary wall	12%	Unknown**	Unknown**	Unknown**	Unknown**

*IVST: interventricular septal thickness

**Case 7 and case 8 transferred.

interventricular septum in echocardiography. **Figure 1** is the alteration of electrocardiogram (ECG) of case 1, low voltage was worsening. ECGs of all 8 patients showed similarly low QRS voltage.

In case 2, cardiovascular MRI was performed and the enhancement of gadolinium was recognized **(Fig. 2)**. In immunofluorescences study, 3 patients were found to have monoclonal immunoglobulin light chains in both the serum and urine, and 5 patients in the urine only. In pathological findings, amyloid was deposited mainly on the mesangium in 6 cases. In 1 patient (case 5), it was possible to diagnose AL amyloidosis on the renal pathology findings alone.

In comparison with the area of amyloid deposition, there was no significant correlation between the degree of proteinuria and renal prognosis. The kappa: lambda light chain antibody ratio was 2 : 6.

Bone marrow aspiration was carried out in all 8 patients, leading to a diagnosis of moclonal gammopathy of undetermined significance (MGUS) in 6 patients, and a diagnose of multiple myeloma in 1 patient. Two patients (case 3 and 6) received high-dose melphalan with autologous peripheral blood stem cell transplantation (HDM/SCT). The proteinuria disappeared and renal functions are maintained. These 2 patients are currently in remission of urinary findings. Case 2 recieved dexamethasone (DEX) because of hepatic involvement prognosis, with a resultant decrease in proteinuria.

Case 1 and 5 were given oral melphalan and prednisone (MP), but this treatment was discontinued after it

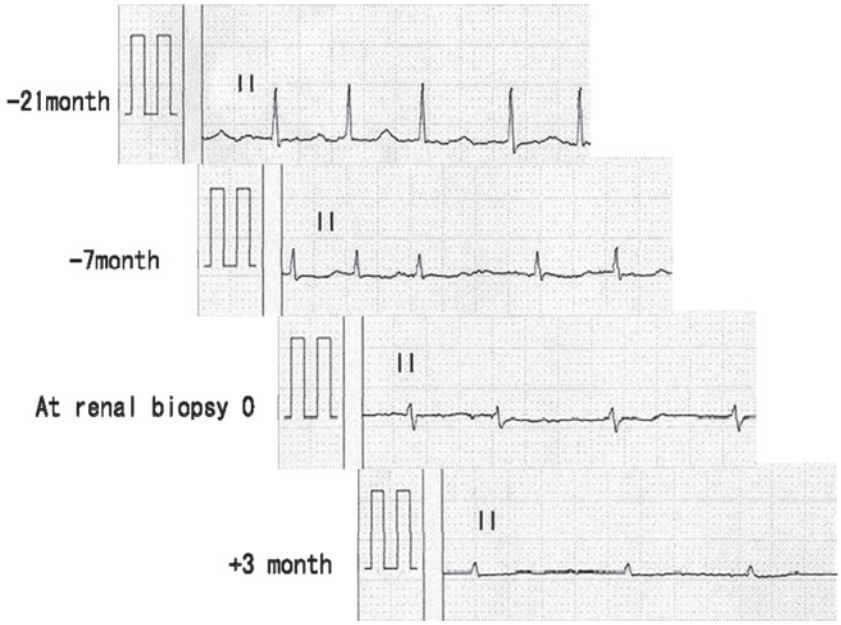

Fig. 1 Time-dependent electorocardiogram of case 1

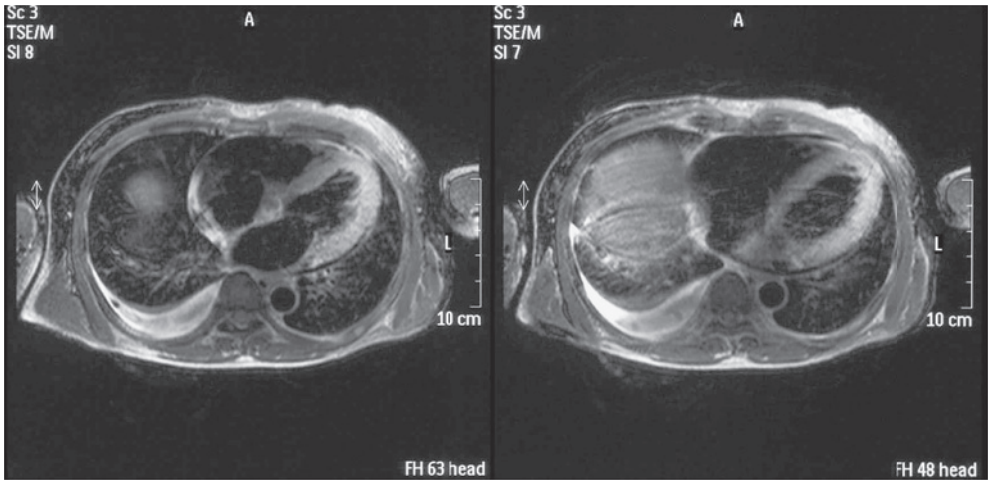

Fig. 2 Cardiovascular magnetic resonance imaging with gadolinium of case 2

failed to improve their condition. Their general status gradually deteriorated, and they died suddenly about 2 months and 8 months after renal biopsy, respectively, following further treatment with the extracorporeal ultrafiltration method (ECUM) and hemodialysis (HD).

Consideration

All of the patients in this study had AL amyloidosis accompanied by nephrotic syndrome and cardiac involvement, and this indicates a bad prognosis. However, not all cases of AL amyloidosis are reported to be associated with nephrotic syndrome, and in these histopathological examination, hematoxylin-eosin sections is nearly normal. If there is any suspicion of amyloidosis, but renal biopsy is not indicated, a needle biopsy of other organs or immunologic tests should be done.

DEX and HDM/SCT are effective in decreasing proteinuria levels and restoring renal function. Especially, HDM/SCT could remit urinary findings and hematologic.

Early and accurate diagnosis of AL amyloidosis is important in selecting and starting treatment. Appropriate treatment of AL amyloidosis could improve prognosis.

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