Case Report

Pathologic improvement after high-dose melphalan and autologous stem cell transplantation for primary systemic amyloidosis

Junichi Hoshino¹, Yoshifumi Ubara¹, Kenichi Ohashi², Fumi Takemoto¹ and Kenmei Takaichi¹

¹Nephrology Center and ²Department of Pathology, Toranomon Hospital, Tokyo, Japan

Abstract

Although primary systemic amyloid light-chain amyloidosis was considered intractable, recent advances in therapy have been reported to result in better clinical outcomes including remission of nephrotic syndrome. However, changes in renal pathologic findings after high-dose chemotherapy have not been characterized. We describe a patient who underwent serial renal biopsies and had complete remission after high-dose melphalan and autologous stem cell transplantation for this form of amyloidosis. Successive renal biopsy specimens showed reduction in amyloid staining mainly in interlobular arterial and arteriolar walls. Thus, amyloid light-chain amyloidosis resolved both clinically and pathologically after high-dose chemotherapy.

Keywords: AL amyloidosis; autologous stem cell transplantation; high-dose melphalan; pathologic improvement

Introduction

Prognosis in primary systemic amyloid light-chain (AL) amyloidosis is generally poor, with an overall median survival for untreated patients after diagnosis of 12 months and <5 months for those with cardiomyopathy [1,2]. Beginning in the early 1990s, favourable responses of AL amyloidosis to high-dose melphalan combined with autologous stem cell transplantation (HDM+SCT) have been reported with descriptions including haematologic and organ responses [3,4]. However, renal pathologic changes after HDM+SCT have not been reported. We therefore characterized a patient with primary systemic AL amyloidosis, including renal involvement, who underwent HDM+SCT. Pathologic changes were compared between successive renal biopsy specimens over 2 years.

Case report

On 4 February 2004, a 56-year-old man was referred for admission to our hospital because of worsened nephrotic syndrome and weight loss. Laboratory test results on admission were total protein, 5.4 g/dL; serum albumin, 2.5 g/dL; s-UN, 9 mg/dL; s-Cr, 0.6 mg/dL; alkaline phosphatase (ALP), 347 IU/L and urinary protein excretion, 5.36 g/day. Polyneuropathy and septal myocardial hypertrophy (13 mm) were also observed. To elucidate the cause of nephrotic syndrome, skin, fat and open renal biopsies were performed on 3 March 2004. The renal biopsy specimens showed amorphous periodic acid-Schiff (PAS)-positive, Congo red-positive and direct fast scarlet (DFS)-positive deposits in the mesangium, glomerular vascular pole, tubulo-interstitium and walls of interlobular arteries and arterioles (Figure 1A and B). These deposits were present in all 23 glomeruli (100%) and 29 of 38 arterial and arteriolar walls (76%), in which 22 walls had circumferential deposits. These deposits show characteristic apple-green birefringence in polarized light and potassium permanganate resistance. Immunohistologic staining was positive for amyloid P and negative for amyloid A. These deposits were also observed in skin, adipose tissue and gastric biopsy specimens. Bone marrow aspirates showed a slight excess of plasma cells without abnormal morphology. We diagnosed him with primary systemic AL amyloidosis of λ (lambda) type.

Beginning in February 2004, the patient received two courses of VAD (vincristine, 0.4 mg/day, and doxorubicin, 9 mg/m²/day, on Days 1–4, and dexamethasone, 40 mg/day by infusion on Days 1–4, 9–12 and 17–20), with the second course initiated 4 weeks later. After the second course, the granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously at 10 g/kg/day for 4 days to mobilize haematopoietic stem cells in the peripheral blood, and 3.35 × 10⁶/kg CD34-positive cells were collected.

On 20 September 2004, melphalan (230 mg or 140 mg/m²) was administered intravenously; 7 days later, cryopreserved stem cells were infused just after thawing. After these therapies, proteinuria was gradually abating (Figure 2): 5.91 g/day on 24 December 2004; 0.85 g/day on 7 March 2005 and 0.12 g/day on 11 January 2006. Serum albumin increased from 1.9 g/dL

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Systemic AL amyloidosis: pathologic improvement

Fig. 1. (A–D): Light microscopic examination of the first renal biopsy specimen showed amorphous PAS-positive and direct fast scarlet (DFS) positive deposits in the mesangium, glomerular vascular pole, tubulo-interstitium, and walls of interlobular arteries and arterioles. DFS reagent staining; original magnification ×200 (A, B); ×400 (C, D). (E–H): Light microscopic examination of the second renal biopsy specimen showed mottled areas of disappearance of amyloid deposits in interlobular arterial walls and arteriolar walls (green arrow). Deposits in the mesangium and glomerular vascular pole also were less extensive and stained less intensely by DFS. DFS reagent staining; original magnification ×200 (E, F); ×400 (G, H). Comparison of amyloid fibrils by electron microscopic examination between first (I) and second (J) renal biopsy specimens. Randomly arranged fibrils (10–12 nm in diameter) were slightly obscured 2 years after treatment. ×75 000 (bar = 100 nm).

Fig. 2. Clinical course.

on 26 July 2004 to 2.2 g/dL on 7 March 2005 and 3.4 g/dL on 11 January 2006. Monoclonal protein in both serum and urine continued to be negative on immunofixation after therapies.

On 15 January 2007, the patient was readmitted to our hospital for follow-up evaluation. Laboratory findings on admission were total protein, 6.0 g/dL; serum albumin, 3.5 g/dL; s-UN, 21 mg/dL; s-Cr, 1.0 mg/dL; AST, 25 IU/L; ALT, 25 IU/L and ALP, 480 IU/L. Urinary protein excretion was 0.03 g/day. Echocardiography showed a decrease in septal myocardial hypertrophy from 13 mm to 9 mm. Nerve conduction velocity examination still showed polyneuropathy. Complete haematologic and clinical responses (cardiac, renal, gastrointestinal and factor X response) were evident according to the criteria described by Skinner et al. [4] and Gertz et al. [5]. A second renal biopsy was performed about 2 years following the first. The specimen showed a mottled reduction in amyloid staining in interlobular arterial walls and arteriolar walls. Furthermore, decreased amounts and intensities of Congo red and DFS staining were observed in the mesangium and glomerular vascular pole (Figure 1C and D). We scored all glomeruli and vascular walls in each sample. Amyloid-positive glomeruli were decreased from 100% to 89% (16 of 18 glomeruli) and amyloid-positive vascular walls were decreased from 76% to 50% (6 of 14 walls). By electron microscopic examination, small electron-dense deposits were seen in the subepithelial region. However, randomly arranged fibrils, characteristic of amyloid, were slightly obscure (Figure 1F). A gastric biopsy specimen also disclosed the disappearance of amyloid deposition. Thus, these therapies resolved AL amyloidosis not only clinically but also pathologically in our patient.
Discussion

We treated a systemic AL amyloidosis patient with HDM+SCT, resulting in a complete clinical response; after 2 years, renal pathologic improvement and disappearance of amyloid deposits in a gastric biopsy specimen were observed. The follow-up renal biopsy specimen showed reduction in amyloid staining mainly in the vascular wall rather than in glomeruli, where resolution of κ and λ amyloid staining in both arterioles and glomeruli was observed. This suggests differences in mechanisms and influences upon proteinuria between glomerular and arteriolar amyloid deposition.

In conclusion, our patient is the first reported to show pathologic improvement of AL amyloid deposition after HDM+SCT. Although systemic AL amyloidosis is still a very serious disease, the new intensive treatment has a goal of not only regression of disease progression but also achievement of complete clinical remission. Gratifyingly, the present case demonstrated the possibility of pathologic improvement after treatment. Much uncertainty persists as to mechanisms and timing of the disappearance of AL amyloid deposition, as well as differences among individual patients. This report should offer valuable information concerning these aspects of the disease.

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Conflict of interest statement. None declared.

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