Clinical and histological responses of renal amyloidosis to high-dose melphalan supported by autologous stem cell transplantation

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Introduction

Primary amyloidosis (AL) is a clonal plasma cell dyscrasia. Monoclonal immunoglobulin light or heavy chain fragments produced by abnormal plasma cells deposit in multiple organs, such as the kidneys, heart and gastrointestinal tract, resulting in severe multi-organ dysfunction. The principal clinical manifestation due to renal involvement is massive proteinuria, which leads to nephrotic syndrome and subsequent renal failure [1,2]. The therapeutic strategy for AL has progressed in parallel with that of multiple myeloma (MM), which is a malignant type of plasma cell disorder. Recently, high-dose chemotherapy with autologous stem cell transplantation (HDT/SCT) has been applied to MM, with a much better outcome than conventional therapy [3]. Thus, this therapy has been further applied to AL, and meta-analysis reveals that 50–75% of renal AL patients treated with HDT/SCT showed more than 50% reduction in proteinuria [4,5].

In spite of many reports of HDT/SCT on AL, the underlying mechanisms for renal responses have not been well identified. Although Zeier et al. [6] described no regression of renal amyloid masses in AL patients responding to this therapy, the local alteration of amyloid depositions was not examined. In this case report, we provide histological evidence for the effectiveness of HDT/SCT that is closely associated with the clinical manifestation of reduced proteinuria.

Case

Clinical course until first renal biopsy

A 56-year-old woman was transferred to our hospital in December 2003 for intensive treatment of nephrotic syndrome due to AL. Other than a uterine myomectomy at age 49, her past and family medical histories were unremarkable. Three years prior to admission, she noticed oedema in her legs and was found to have proteinuria. Renal AL was confirmed, and chemotherapy with melphalan and prednisolone was initiated 1 year prior to her transfer to our hospital. However, proteinuria had continued, with oedema developing further.

On admission, physical examination determined a temperature of 36.7 °C, heart rate of 66 bpm and blood pressure of 125/80 mm Hg. She weighed 55.8 kg and was 158 cm tall. There was palpable oedema in the lower extremities. There were no macroglossia, lymphadenopathy, hepatosplenomegaly, neurological abnormality, muscle atrophy or skin changes.

Laboratory findings showed the following values: creatinine, 0.5 mg/dl (44 μmol/l); blood urea nitrogen, 7.8 mg/dl (2.8 mmol/l); creatinine clearance, 109 ml/min (1.82 ml/s); albumin, 20 g/l; total protein, 43 g/l and total cholesterol, 349 mg/dl (9.03 mmol/l). Immunoglobulins in the plasma were immunoglobulin G (IgG), 531 mg/dl (5.31 g/l); IgA, 250 mg/dl (2.5 g/l) and IgM, 127 mg/dl (1.27 g/l). Immunoelectrophoresis revealed the presence of paraproteins as the Bence Jones type, with λ light chains in both serum and urine. Urinalysis showed excretion of urinary protein (4+;
11 g/day) and hyaline casts. Urinary red blood cells were absent. Electrocardiogram and transthoracic echocardiogram showed no clinical signs, suggesting AL in the heart. Endoscopic examination of the stomach and large intestine revealed no abnormalities. A bone marrow aspiration demonstrated normocellular marrow with slightly enlarged plasma cells (8.2% of the total number).

Pathological findings in first renal biopsy (Figure 1A and B)

A percutaneous renal biopsy was performed on hospital Day 2 to confirm the diagnosis, and to examine the expanded level of amyloid depositions (first biopsy). The renal specimen included 16 glomeruli. All showed widened mesangial areas revealing periodic acid-Schiff positive depositions of homogeneous acellular material, which had an affinity for Congo red staining (Figure 1A). Deposits were distributed both in the capillary walls and mesangial areas. Mesangial cellularity was normal. On silver staining, subendothelial deposits formed perpendicular projections on the epithelial side of the basement membranes (Figure 1B).

HDT/SCT therapy and following clinical course

Although the patient developed resistant nephrotic syndrome due to renal AL, examinations revealed that organ dysfunction based on the amyloid depositions was specifically limited to the kidneys. Therefore, we performed HDT/SCT twice over the course of 6 months. Peripheral blood stem cell (PBSC) mobilization was induced, using the granulocyte-colony-stimulating factor. PBSCs were assessed by quantifying the CD34-positive cells. The patient did not receive any chemotherapy between PBSC collections. For pretreatment cytoreduction, only high-dose melphalan was administered over two consecutive days for a total dosage of 200 mg/m². Two days later, PBSCs (7.6 × 10⁹/kg) were infused. The patient also received blood products and antibiotics. Although the excreted amount of paraproteins in the urine was reduced, the levels of urinary protein and serum albumin were unchanged 3 months after the first HDT/SCT therapy.
However, after the second treatment, paraproteins were undetectable in both serum and urine. Urinary protein decreased to 9 g/day, and the serum albumin level increased to 28 g/l over several months after the second HDT/SCT. Two years later, a follow-up renal biopsy was performed (second biopsy). Urinary excretion of protein had reduced to 2.39 g/day, while serum albumin and total protein levels had increased to 30 and 51 g/l, respectively. Electrophoresis demonstrated the absence of paraproteins in both serum and urine. The serum creatinine level was 0.6 mg/dl (53 µmol/l), with a creatinine clearance of 88 ml/min (1.47 ml/s). A year after the second biopsy, urine protein had further reduced to 1.8 g/day, and the plasma albumin level had increased to 39 g/l.

Pathological findings of second renal biopsy (Figure 1C and D)

The renal specimen included 20 glomeruli, eight of which were globally sclerosed. In the remaining glomeruli, periodic acid-Schiff positive depositions, which had an affinity for Congo red staining, were noted again in both the mesangial areas and capillary walls. Although the amounts of amyloid deposits in the mesangial areas were quite similar to those of the first biopsy (before HDT/SCT therapy), the deposit staining in the capillary walls appeared to be reduced (Figure 1C). On silver staining, spicular arrangements along the outer aspect of the capillary walls were diminished (Figure 1D). In the tubulo-interstitial space, focal tubular atrophy was observed around the glomeruli with global sclerosis.

Quantitative analysis of amyloid deposition in the glomeruli (Figure 2)

Amyloid deposits in the glomeruli were quantitatively measured by image analysis (NIH image, National Institute of Health). Depositions (Figure 2A) in the glomeruli were classified as pericapillary depositions (indicated by red: C) and mesangial depositions (indicated by yellow: M), which were individually measured. The distribution ratio of pericapillary deposits to total deposits (C/C + M) was calculated for each glomerulus. These values of the first (before HDT/SCT therapy) and the second (after HDT/SCT therapy) biopsy specimens are demonstrated in Figure 2B. Although M values were quite similar for both, the C/M ratio of the second biopsy was significantly reduced compared to that of the first.

Discussion

Our present case showed more than a 50% reduction in proteinuria, a marked elevation of plasma albumin concentration, a stable plasma creatinine level and the disappearance of paraproteins in both serum and urine. Therefore, this patient is considered to have shown a good response [4,5]. The follow-up renal biopsy performed 2 years after HDT/SCT therapy demonstrated a reduction of amyloid depositions in peripheral capillaries in glomeruli, as manifested by the disappearance of pericapillary spicular formation on silver staining, though depositions in the mesangial areas remained unchanged. This reduction of depositions in the glomerular capillaries was further quantitatively confirmed by image analysis. These findings indicate that HDT/SCT has therapeutic effects on both clinical manifestations and pathological lesions of AL. The most characteristic histological feature of renal AL is abnormal immunoglobulin depositions in glomeruli and vascular walls, which have a strong affinity for Congo red staining. Particularly, depositions on glomerular capillary walls are defined as spicular formations on silver staining: argyrophilic perpendicular projections on the epithelial side of the glomerular basement membranes. As these amyloid depositions in the glomeruli morphologically vary both in location and quantity, some studies have reported the lack of a close relationship between the degree of proteinuria and the extent of amyloid depositions [7,8]. Shiiki et al. [9,10] however, found that deposits in glomerular capillaries contributed to structural damage in the basement membranes, leading to the escape of plasma protein into the urine, even when the total amount of depositions was small. Our patient demonstrated a reduction of glomerular capillary depositions and a decrease in proteinuria after HDT/SCT therapy. Therefore, the present findings provide further evidence of an association between glomerular capillary deposition and proteinuria.
In conclusion, the present case demonstrates the clinical effectiveness of HDT/SCT for renal amyloidosis by a reduction of glomerular capillary deposition. The clinical course also suggests that a long period is required for this reduction after the disappearance of circulating paraproteins.

Conflicts of interest statement. None declared.

References


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