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[Case Report]

A LONG-TERM REMISSION OF RENAL AMYLOIDOSIS WITH NEPHROTIC SYNDROME AFTER AUTOLOGOUS PERIPHERAL BLOOD STEM-CELL TRANSPLANTATION

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Abstract : Renal amyloidosis is typically characterized by nephrotic syndrome, often with massive proteinuria and refractory peripheral edema. We report the case of a patient with renal amyloidosis associated with nephrotic syndrome who maintained remission for 6 years after undergoing high-dose chemotherapy followed by autologous peripheral blood stem-cell transplantation (auto-PBSCT). The patient was a man aged in his 50s who had developed nephrotic syndrome. Bone marrow aspiration and kidney biopsy determined that the cause of the nephrotic syndrome was renal amyloidosis due to multiple myeloma, and the patient was admitted to our department in July 2003. After one course of chemotherapy, auto-PBSCT was performed in March 2004. Following transplantation, serum M-protein was no longer detectable from March 2005, and the patient achieved complete hematological remission. Subsequently, proteinuria decreased, serum albumin levels normalized, and nephrotic syndrome improved. As of 6 years after transplantation, in March 2010, the patient remained in remission, meaning that auto-PBSCT proved extremely effective as a treatment for renal amyloidosis in this case.

Key words : renal amyloidosis, nephrotic syndrome, PBSCT, multiple myeloma

INTRODUCTION

Amyloidosis is an intractable disease in which amyloid fibril proteins are deposited in organs such as the heart, kidneys, liver, and digestive tract, causing various forms of damage. Among the different types, AL amyloidosis is caused by amyloid fibril proteins derived from monoclonal immunoglobulin (M-protein) light chains and is a type of plasma cell dyscrasia such as multiple myeloma. Prognosis is poor, with median survival without treatment of approximately 1 year, and <5 months for cardiac amyloidosis in particular[1,2)]. In most cases, two or more organs are symptomatic at the time of diagnosis, with kidney damage present in approximately 70% of cases. The kidneys are the organs most effectively invaded. Renal amyloidosis produces symptoms such as proteinuria and nephrotic syndrome in many cases[1)]. A report from Italy estimated the rate of onset of renal amyloidosis as 2.1

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new cases per million people[3]. In Japan, this condition accounts for 0.2% of the original kidney disease in dialysis patients[4]. High-dose chemotherapy followed by autologous peripheral blood stem-cell transplantation (auto-PBSCT) is a useful treatment for AL amyloidosis. Dember, *et al.* reported that proteinuria decreased during a two-year follow-up period in 36% of patients with renal amyloidosis who underwent auto-PBSCT[5]. In the case reported here, high-dose chemotherapy followed by auto-PBSCT was performed in a patient with severe nephrotic syndrome due to renal amyloidosis associated with multiple myeloma, in whom hematological remission and improvement of nephrotic syndrome have been maintained over a period of 6 years.

CASE REPORT

The patient was a man in his 50s. He had undergone annual health checks since his 40s, but no abnormalities had been identified. In November 2002, M-protein was identified in his serum and he was referred to our department. Immunoelectrophoresis detected immunoglobulin (Ig) G-λ-type M protein in serum. As bone marrow aspiration found 10% plasma cells in bone marrow and no bone lesions were observed, stage I multiple myeloma was diagnosed (Durie & Salmon)[6] and a policy of observation was followed. Serum albumin level gradually declined, so he underwent kidney biopsy for suspected nephrotic syndrome in May 2003. Amyloid deposition was diagnosed in Congo red-stained section of kidney biopsy specimen by the presence of apple green birefringence under polarized light microscopy as well as by the demonstration of characteristic amyloid fibrils on electron microscopy (Fig. 1). It was diagnosed AL amyloidosis (renal amyloidosis) by these results and the patient was re-admitted to our department for treatment in July 2003. Complete blood count results showed no anemia, white blood cell count, 8,600/μl ; hemoglobin, 14.5 g/dl ; and platelets, 22.5×10^4/μl. The urinary sediment contained 5 to 9 erythrocytes and 1 to 4 leukocytes per high-power field, plus several hyaline casts. Blood biochemistry testing did not show hypergammaglobulinemia or renal dysfunction, but severe hypoalbuminemia was present, with : total protein, 5.9 g/dl ; IgG, 1,690 mg/dl ; IgA, 82 mg/dl ; IgM, 22 mg/dl ; urea nitrogen, 10 mg/dl ; serum creatinine, 0.8 mg/dl ; creatinine clearance, 76.4 ml/min ; and serum albumin, 2.0 g/dl. In urinalysis, a 24-h specimen of urine contained 4.2 g of protein, indicating nephrotic

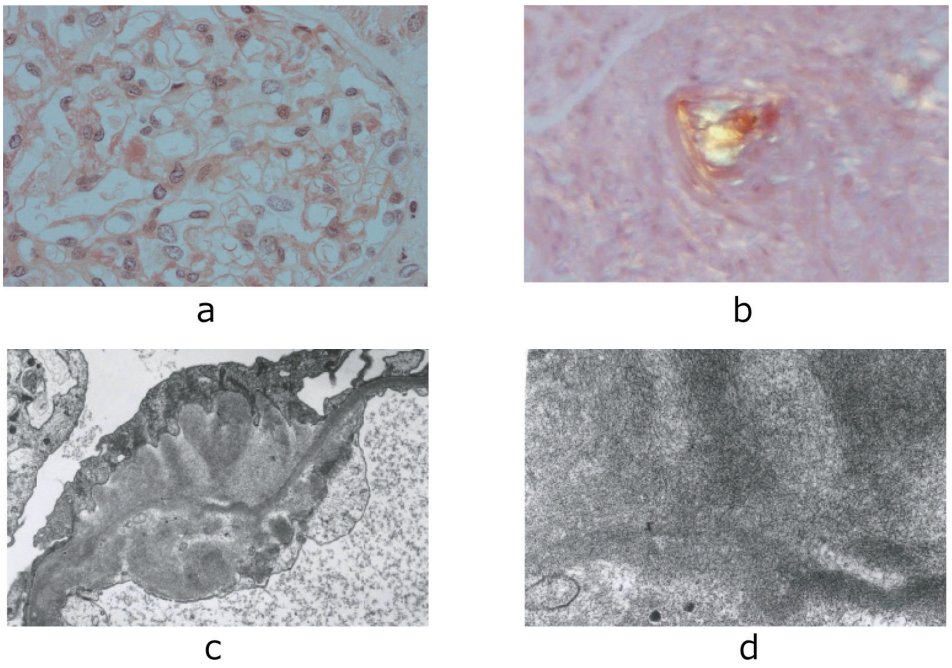

Fig. 1. Histology of kidney biopsy
(a) Amyloid reacting to Congo-red stain in the glomerular capillary wall and mesangial area (original magnification, ×400), (b) The detection of polarized apple-green light in the vessel walls of arteriole under polarizing microscope (original magnification,×200), (c) The detection of transmembranous deposits under electron microscopy (×6,500), (d) This electron micrography demonstrates relatively straight, nonbranching and randomly rearranged amyloid fibrils (×25,000).

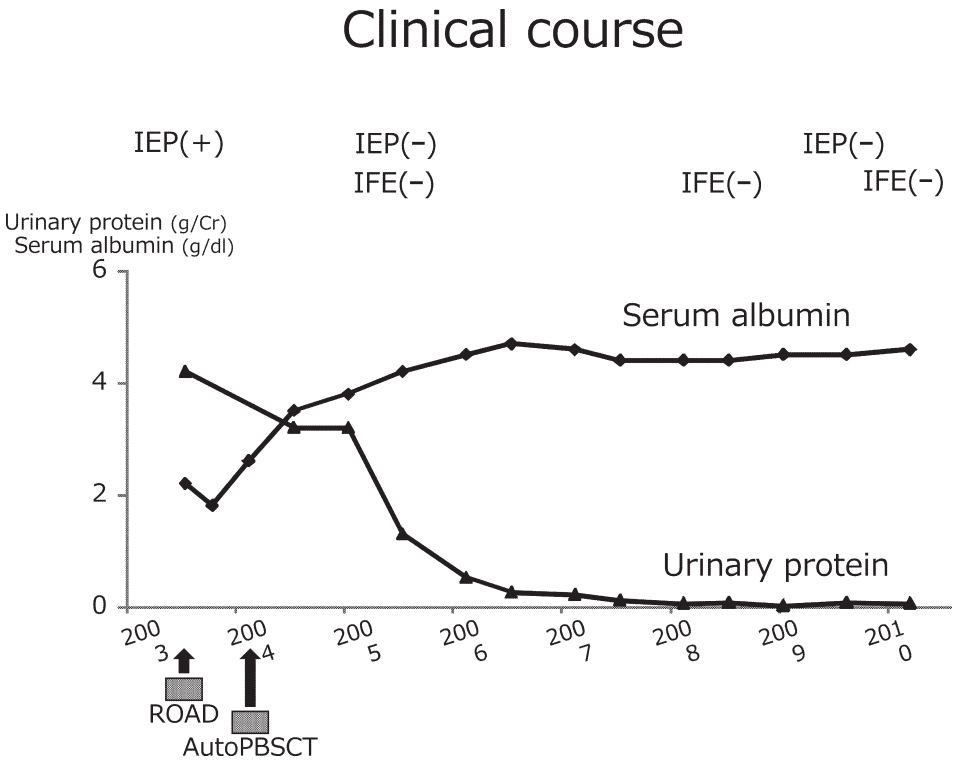

Fig. 2. Clinical course of the patient
IEP, immunoelectrophoresis ; IFE, immunofixation electrophoresis

syndrome. Immunoelectrophoresis confirmed the presence of IgG-λ type M-protein in serum and Bence Jones-λ type M-protein in urine. The percentage of plasma cells in bone marrow was 18%, with most cells showing positive immunostaining for λ light chains. Amyloid depositions were also verified on the gastric and rectal mucosa. No findings of cardiac amyloidosis were identified. Chemotherapy with ranimustine, vincristine, melphalan, and dexamethasone (ROAD therapy)[7] was administered from July 2003 (Fig. 2), but the serum albumin level continued to decrease. As the patient then refused any further continuation of chemotherapy, his course was monitored for 6 months without treatment. He then agreed to undergo auto-PBSCT and was readmitted in February 2004. Peripheral blood stem cells were mobilized with granulocyte colony-stimulating factor after administration of etoposide at 500 mg/m^2, and 6.9×10^6 cells/kg of CD34-positive cells were harvested. In March 2004, auto-PBSCT was performed after administering 200 mg/m^2 of melphalan. Engraftment was obtained on day 10 post-transplantation, and he was discharged on day 18. In March 2005, M-protein was no longer detected even on immunofixation electrophoresis, and as amyloid fibril proteins were also no longer detectable from the gastrointestinal tract, the patient was determined to have achieved complete remission from multiple myeloma. Proteinuria subsequently decreased, serum albumin level normalized in 2005, and the nephrotic syndrome improved. Complete remission has been maintained for 6 years.

DISCUSSION

AL amyloidosis is occasionally characterized by deposition in the peribasement membrane. Bohle, et al. reported that tubulointestinal damage in renal amyloidosis, and especially fibrosis, is an important determination of renal prognosis[8,9]. The rate of progression to renal failure is usually slow, but depends directly on the intensity of proteinuria and extension of amyloid deposits, especially in the vessels and tubules[10]. Three potential treatment strategies are used for AL amyloidosis : 1) suppression of secretion of amyloid fibril proteins from plasma cells, 2) destruction of the plasma cells secreting amyloid fibril proteins, and 3) promotion of the proteolysis of amyloid fibril proteins. As no effective treatment methods for suppressing secretion or promoting proteolysis have been identified, destruction of secretory cells is currently the main current target of clinical treatment. Treatment

with melphalan and prednisolone (MP therapy) has been carried out for some time with the objective of destroying myeloma cells, which secrete amyloid fibril proteins, but the response rate is only 20–25%, median survival is 18 months, and 5-year survival rate is 15%, meaning that this treatment cannot be considered successful[11]. High-dose dexamethasone therapy offers a higher response rate than MP therapy and median survival is 31 months, but the incidence of grade 3 or greater toxicities is 51%[12,13]. Median overall survival for combined therapy with melphalan and dexamethasone is 5.1 years, with a progression-free survival of 3.8 years. At present, this combined therapy is recommended as the first-choice treatment for patients who are ineligible for auto-PBSCT[14,15]. At this point, high-dose chemotherapy followed by auto-PBSCT, as used for the patient described here, is regarded as the most effective treatment for patients who meet the criteria. We performed auto-PBSCT on this patient in 2004, the same year in which a report from Boston University described the results of 312 cases with auto-PBSCT[16]. According to that report, hematological response was obtained in 76% of patients, including 36% who achieved complete remission (CR), with organ improvement observed in 66%. Median survival was 4.6 years. Dember, *et al.* reported in 2001 that they used auto-PBSCT to treat 65 renal amyloidosis patients exhibiting proteinurea of ≥1 g/24 h, with a decrease in proteinurea of ≥ 50% in 36% of patients over a two-year follow-up period. In patients with complete hematological response, median 24-hour urinary protein excretion decreased from 9.6 g/24 h before treatment to 1.6 g/24 h and 1.4 g/24 h at 12 and 24 months, respectively[5]. The mechanism by which auto-PBSCT reduces proteinurea in renal amyloidosis is not well understood. Auto-PBSCT treatment is capable of promptly suppressing production of M-protein and organ deposition of amyloid fibril proteins, but the elimination of the amyloid fibril proteins that have already been deposited in organs is required for the improvement of organ damage seen in the present patient. Amyloid fibril proteins deposited in tissue are surrounded by multi-nucleated giant cells, and cathepsin K, found within these cells, is known to degrade amyloid fibril proteins[17]. In addition to cathepsin K, the macrophage-derived cysteine proteases cathepsin B and cathepsin L have also been reported as degrading amyloid fibril proteins[18]. A mechanism thus exists for metabolizing amyloid fibril proteins after deposition into tissue. In other words, if new amyloid fibril protein production can be completely suppressed for a given period of time by high-dose chemotherapy, amyloid fibril proteins deposited in tissue may be eliminated.

Subsequent to the case described here, we also performed auto-PBSCT on a patient with cardiac amyloidosis who had developed life-threatening arrhythmia[19]. As a cause of death, arrhythmia is one of the most important complications of cardiac amyloidosis. Since ventricular tachycardia and ventricular fibrillation occurred frequently in this patient we performed auto-PBSCT after implantation of a cardioverter-defibrillator (ICD). Diastolic function improved after transplantation, with no inappropriate shocks by the ICD during more than 4 years of post-transplantation follow-up. That case indicates the possibility that auto-PBSCT may have the effect of preventing death from lethal arrhythmias in amyloidosis patients with cardiac lesions.

According to a report from Boston University, improvements in amyloidosis-related renal dysfunction were seen in 63% of patients in whom complete hematological remission was achieved within 1 year after transplantation, but improved renal function was seen in only 11% of patients who did not achieve complete remission[16]. We have so far performed auto-PBSCT on 7 patients with AL amyloidosis, and all patients with improved organ function after transplantation were those who achieved hematological remission. M-protein also disappeared from serum within 1 year after transplantation in the patient described in this study, and such a prompt hematological response can be regarded as contributing to the improvement in nephrotic syndrome. This patient had undergone ROAD therapy before transplantation, and the fact that the tumor mass had reduced to some extent before transplantation may possibly have resulted in the prompt improvement. Combined use of thalidomide, bortezomib, and lenalidomide offers a new formulation that has been shown to be useful in the treatment of multiple myeloma, and utility for the treatment of AL amyloidosis is under investigation[20–22]. Production of inflammatory cytokines via NF-κB activation is known to be related to the onset of renal lesions in myeloma and renal amyloidosis. The end result is apoptosis of tubular cells, persistent inflammation and progressive fibrosis leading to irreversible end-stage renal failure. Bortezomib may contribute to improving kidney disease, including renal amyloidosis through the inhibition of NF-κB[23]. Use of the chemotherapy administered to the patient in this study or new formulations before and after transplantation might

enable prompt achievement of post-transplantation hematological remission. The most serious problem with auto-PBSCT is the large number of transplant-related deaths. In the Boston University study, the post-transplantation 100-day mortality rate was 13%. In consideration of the indications for transplantation, future study is required into what subgroup of AL amyloidosis patients will benefit from transplantation therapy. The patient we described has maintained remission with no recurrence for 6 years after transplantation, but analysis of a large number of cases is required to clarify the sort of patients in whom such long-term remission can be achieved.

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