High dose Chemotherapy and Stem Cell Support in a Patient of Light- and Heavy-chain Deposition Disease with Abnormal Marrow Cell Surface Antigens and No Monoclonal protein

Masanori SAKAKIMA, Yoshihide FUJIGAKI, Takayuki TSUJI, Hirotaka FUKASAWA, Takehiko MIYAJI, Kensuke NAITO**, Tatsuo YAMAMOTO, Katsuhiko YONEMURA*, Kazunori OHNISHI** and Akira HISHIDA

Abstract

A 53-year-old man with nephrotic syndrome and severe renal failure was diagnosed with light- and heavy-chain deposition disease (LHCDD) by renal biopsy. The patient had no monoclonal protein and mild marrow plasmacytosis (6%), but marrow plasma cells expressed CD19⁺CD56⁺ and predominant monoclonal kappa-chain, indicating plasma cell dyscrasia. Conventional chemotherapy was ineffective and did not improve renal failure. High dose chemotherapy/peripheral blood stem cell transplantation (HDC/PBSCT) was introduced even after hemodialysis to eliminate aberrant clone and normalization of bone marrow cell surface markers. Immunophenotypic analysis of marrow cells facilitates clinical decision making regarding the use of HDC/PBSCT for LHCDD patients without monoclonal protein. (Internal Medicine 44: 970–974, 2005)

Key words: hemodialysis, light- and heavy-chain deposition disease, marrow cell surface antigens, monoclonal protein, peripheral blood stem cell transplantation, renal failure

Introduction

Light- and heavy-chain deposition disease (LHCDD) was first reported in 1980 by Preud'homme et al (1), and is characterized by deposition of both monoclonal immunoglobulin

light- and heavy- chains in several body organs. LHCDD belongs to the disease entity of monoclonal immunoglobulin deposition disease (MIDD) together with light-chain deposition disease and heavy-chain deposition disease (2), and an apparent clinical difference has not been reported among them. MIDD involves the kidneys most frequently, where patients present with proteinuria and renal insufficiency (2). Renal function deteriorates rapidly in most patients to end-stage renal disease, and the reported patient survival is rather poor even in those who receive early and aggressive conventional chemotherapy (3). MIDD is often associated with multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS), but about 20% of MIDD have neither evidence of any overt plasma cell dyscrasia nor the presence of monoclonal protein in the serum or urine (4).

Here, we report a case of renal-biopsy proven LHCDD without monoclonal protein or marrow plasmacytosis (the criterion of malignant myeloma). Analysis of bone marrow cell surface markers suggested plasma cell dyscrasia. Accordingly, high-dose chemotherapy combined with peripheral blood stem cell transplantation (HDC/PBSCT) was considered appropriate. The treatment was successful in our patient who was placed on hemodialysis, resulting in normalization of marrow plasma cell surface markers.

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Case Report

A 53-year-old Japanese man had a history of proteinuria

From the First Department of Medicine, *Hemodialysis Unit, **the Third Department of Medicine, Hamamatsu University School of Medicine, Hamamatsu

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Reprint requests should be addressed to Dr. Yoshihide Fujigaki, the First Department of Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192

Figure 1. Light microscopic examination of renal tissue samples. (A) The glomerulus shows lobular formation and periodic acid-Schiff-positive mesangial nodular lesions (asterisks) with mild to moderate increase in mesangial cellularity at peripheral areas (periodic acid-Schiff stain, $\times 200$). (B) Atrophic tubules with thickening of the tubular basement membranes (arrows) (periodic acid-Schiff stain, $\times 400$).

identified on a routine medical examination at the age of 40 years, but no investigation of the cause was conducted. In February 2003, he noticed body weight gain (10 kg over a 2-month period) and leg edema. On March 28, he was diagnosed as nephrotic syndrome with end-stage renal failure at a peripheral hospital and referred to our center for further investigation. On admission (May 26, 2003), physical examination revealed hypertension of 158/90 mmHg, pale conjunctiva, a grade 1/6 systolic murmur on chest auscultation and pitting edema in both legs. Laboratory tests showed a hemoglobin concentration of 8.3 g/dl, hematocrit of 23.5%, reticulocytes 20%, leukocyte count $10,200/\text{mm}^3$ and platelet count of $48.0 \times 10^4/\text{mm}^3$. Blood chemistry was as follows: serum creatinine 3.2 mg/dl, blood urea nitrogen 31.4 mg/dl, total protein 4.3 g/dl, serum albumin 2.5 g/dl, total cholesterol 325 mg/dl, triglyceride 574 mg/dl, and cholinesterase 276 U/l. Urinalysis revealed proteinuria of 7.2 g/day, slight hematuria but no glucosuria. The creatinine clearance was 38.5 l/day. Serological tests were normal or negative, including C-reactive protein, rheumatoid factor, hepatitis B surface antigen, hepatitis C virus antibody, complements 3 and 4, 50% hemolytic unit of complement, antinuclear antibody, anti-DNA antibody, and cryoglobulin. Immunoglobulin (Ig)G was 443 mg/dl, IgA 94 mg/dl, and IgM 118 mg/dl. Serum and urine protein electrophoresis showed no monoclonal protein. An electrocardiogram showed left ventricular hypertrophy. Chest radiological examination showed mild pleural effusion without cardiomegaly or abnormal shadow in the lung fields. Abdominal echography showed swelling of both kidneys (right 13.4×5.7 cm, left 13.0×5.2 cm) and echocardiography revealed mild left ventricular hypertrophy without apparent sign of deposition.

A renal biopsy was performed on May 29, 2003 to evaluate the nephrotic syndrome. One glomerulus was detected

with global sclerosis and one with fibrocellular crescent formation out of 39 glomeruli obtained. Most glomeruli showed lobular formation and periodic acid-Schiff (PAS)-positive but periodic acid-silver methenamine-negative mesangial nodular lesions with a mild to moderate increase in cellularity at peripheral areas (Fig. 1A). The glomerular capillary walls sometimes showed a partial double contour. Tubular atrophy with thickening of the tubular basement membrane and intimal thickening of small arteries were found (Fig. 1B). There was interstitial fibrosis associated with slight round cell infiltration in about 80% of tubulointerstitial areas (data not shown). Congo-red staining for amyloid was negative (data not shown). Immunofluorescent study was negative for IgA, IgM, C3, C4 and C1q. Mild to moderate staining for IgG was found in the mesangial nodular lesions and along the glomerular capillary walls, Bowman's capsules, the tubular basement membranes and small arteries (Fig. 2A). Identical staining patterns of kappa- and gamma-chains but not lambda-chain were found (Fig. 2B–D). Based on the above laboratory and histopathological findings, the patient was diagnosed as LHCDD. Electron microscopy showed fine granular electron dense deposits along the inner aspect of the glomerular basement membranes, and on the outer side of the tubular basement membranes and the subendothelium of the small arteries; but apparent deposits could not be found in the nodular lesions (Fig. 3A–C).

Biopsies of gastric mucosa and rectal mucosa showed no deposition of light- or heavy-chains. Bone marrow examination showed 6% of plasma cells without morphological abnormalities, but flow cytometric immunophenotypic analysis showed that these cells expressed $\text{CD}19^+ \text{CD}56^+$ (Fig. 4A), which is compatible with the pattern of multiple myeloma that can be distinguished from the pattern of normal plasma cells ($\text{CD}19^+ \text{CD}56^-$) (5). Cytoplasmic light chain analysis of

Figure 2. Immunofluorescent staining for immunoglobulin G (A), gamma-chain (B) and kappa-chain (C) in glomerular mesangial nodular lesions, glomerular capillary walls, Bowman's capsule and tubular basement membranes. Immunostaining for lambda chain (D) is negative. G: glomeruli, T: tubules (A, C, D, $\times 400$; B, $\times 300$).

bone marrow plasma cells revealed that the $\kappa:\lambda$ ratio was 12.5 (Fig. 4B) [the criteria for light chain restriction in the normal population is as follows: monoclonal κ , $\kappa:\lambda$ ratio ≥ 3 ; monoclonal λ , $\kappa:\lambda$ ratio ≤ 0.5 (6)], indicating plasma cell dyscrasia.

To improve renal failure and prevent extrarenal deposition of light- and heavy-chains, we started vincristine-doxorubicin-dexamethasone therapy on July 22, 2003, and the course was repeated three times. However, this treatment produced no beneficial effects on renal function. Although hemodialysis commenced on November 10, 2003, HDC/PBSCT was introduced to eliminate the aberrant clone. The number of CD34+ cells obtained was $2.07 \times 10^6/\text{kg}$ body weight. PBSCT was performed after melphalan (140 mg/m^2) treatment. Granulocyte colony-stimulating factor (G-CSF) ($300 \mu\text{g}$) (Kirin Brewery Co., Tokyo, Japan) was administered subcutaneously, daily from day 1 after PBSCT. On day 11 after PBSCT, the neutrophil count was $500/\text{mm}^3$, and on day 18, the platelet count was $5.0 \times 10^4/\text{mm}^3$ and reticulocytes 10%. This was considered to represent sufficient bone marrow recovery and plasma cell markers after PBSCT showed nor-

malization (Fig. 4C, D). Sixteen months after PBSCT, the patient remains on hemodialysis without any evidence of involvement of LHCDD in other body organs.

Discussion

Reports of LHCDD are rare, but it is considered that LHCDD is a variant of LCDD, showing similar clinicopathological pictures of LCDD (3). Renal dysfunction and proteinuria are the major laboratory and clinical findings at the onset of LHCDD like LCDD. A recent retrospective analysis of 5 patients with LHCDD (3) showed a mean serum creatinine of $5.3 \pm 2.0 \text{ mg/dl}$ ($\pm \text{SEM}$) and proteinuria of $2.9 \pm 1.0 \text{ g/day}$ at the time of renal biopsy, and one patient had multiple myeloma and 3 had MGUS. In other reports of patients with L(H)CDD, about 20% showed no detectable monoclonal protein in the serum and urine by conventional analysis, similar to the present case (4). Considered together, these findings suggest that in most cases with no detectable monoclonal protein, abnormal immunoglobulin molecules are secreted and are either rapidly degraded post syntheti-

Figure 3. Electron microscopic examination showed the presence of fine granular electron-dense deposits (arrowheads) in the inner aspect of the glomerular basement membrane (A), in the outer aspect of the tubular basement membrane (B) and in the subendothelium of small arteries (C). CL: capillary lumen, US: urinary space, PT: proximal tubule, E: endothelial cells. Bars= 3.0 μ m.

cally or deposited in tissues (2).

It is reported that renal and patient survivals were significantly worse in LCDD patients with coexistent myeloma cast nephropathy (mean, 4 and 22 months, respectively), compared with patients with pure MIDD (mean, 22 and 54 months, respectively) (3). However, renal and patient survivals were not influenced by the presence of multiple myeloma in 34 cases of MIDD without myeloma cast nephropathy (3). In another report, analysis of 63 cases of LCDD revealed that the median time from diagnosis to renal death was 2.7 years and the median survival was 4.1 years and that cases with multiple myeloma or with symptomatic extrarenal light chain depositions were associated with a worse outcome than those without (7). MIDD is considered as a systemic disease frequently involving the heart and liver except kidney (7), and cardiac failure or hepatic failure may cause patient death upon progression of the disease (7, 8).

Chemotherapy for multiple myeloma has been applied for cases of MIDD with definite multiple myeloma. However, there is no consensus regarding chemotherapy, with potential severe adverse effects, and whether it should be introduced in cases without definite malignant hematological diseases as in the present case. In recent years, the diagnosis of hemato-

logical malignancy is based not only on morphology but also on immunophenotyping using cell surface markers (5), however, the clinical importance of abnormal cell surface markers without definite malignant hematological diseases has not been clarified. We made a decision to use vincristine-doxorubicin-dexamethasone-therapy in the present patient based on 1) bone marrow cell surface markers, which showed a pattern similar to that of multiple myeloma and plasma cell dyscrasia, 2) the patient was under 60 years of age and 3) the patient showed no evidence of other organ involvement apart from the kidney. In LCDD, it is reported that chemotherapy resulted in the reduction of proteinuria, improvement of renal function and disappearance of glomerular nodular lesions 7 months after the treatment (9), however, hemodialysis had to be introduced in the present case because of no apparent benefit of the therapy.

Autologous PBSCT is one of the therapeutic options in selected patients with multiple myeloma and AL-amyloidosis even with renal involvement, and a favorable remission rate has been reported (10–12). To date, few patients with L(H)CDD have been treated with HDC/PBSCT. Recently, Royer et al treated 11 patients with L(H)CDD by HDC/PBSCT, who were under 65 years of age, including 4

Figure 4. The surface expression of CD19 and CD56 (A, C), and intracellular expression of kappa and lambda chains (B, D) in bone marrow plasma cells before (A, B) and after HDC/PBSCT (C, D). Marrow plasma cells were identified using CD38 fluorescence and side-scatter gating, then unstimulated isolated marrow plasma cells were stained with both anti-CD19 and anti-CD56 monoclonal antibodies (A, C), and both anti-kappa chain and anti-lambda chain monoclonal antibodies (B, D), and analyzed using flow cytometry. The percentages of cells are shown in each of the quadrants.

dialysis cases. They reported that no toxic death occurred and the reduction of the monoclonal protein level in 8 cases with complete disappearance from serum and urine in 6 cases and improvement in organ dysfunction related to monoclonal immunoglobulin deposits in 6 cases (13). The present patient underwent hemodialysis 16 months after HDC/PBSCT, however, clones producing abnormal light- and heavy-chains had disappeared because of normalization of cell surface marker abnormalities (Fig. 4). It is necessary to follow-up the patient carefully by monitoring echocardiography and liver enzyme tests for cardiac and hepatic involvement with light- and heavy-chain depositions, since

there is no specific serological markers.

Flow cytometric immunophenotypic analysis of bone marrow plasma cells may facilitate clinical decision making regarding the use of aggressive chemotherapy or HDC/PBSCT in potentially poor survival patients of LHCDD without detectable monoclonal protein.

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