Light-Chain Deposition Disease Successfully Treated with Bortezomib in an Elderly Patient: A Case Report and Review of the Literature

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Abstract

We herein report the case of an elderly patient with light-chain deposition disease (LCDD) successfully treated with bortezomib. An 83-year-old woman was admitted because of nephrotic syndrome. She was diagnosed to have monoclonal gammopathy of undetermined significance (IgG-κ type) and LCDD, on the basis of serum and urinary immunoelectrophoresis and renal biopsy. She responded to a modified regimen of bortezomib-based chemotherapy with disappearance of proteinuria without any adverse effects. According to a literature review of 16 cases, including the present case, bortezomib-based chemotherapy appears to be a convincing strategy for the treatment of LCDD even in elderly patients.

Key words: light-chain deposition disease (LCDD), monoclonal gammopathy of undetermined significance (MGUS), elderly, bortezomib

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Introduction

Light-chain deposition disease (LCDD) is an uncommon disorder characterized by the systemic deposition of monoclonal light chains (LCs) (1). The kidneys are almost always affected, while the heart, liver, and other tissues are occasionally involved (2, 3). LCDD is associated with multiple myeloma (MM) in 58% of patients and monoclonal gammopathy of undetermined significance (MGUS) in 17% (4, 5). The remaining 25% of patients have other lymphoproliferative disorders (e.g., chronic lymphocytic leukemia) or idiopathic lesions (lacking a demonstrable association with other hematologic diseases) (4, 5). The clinical picture consists of hypertension, nephrotic syndrome (NS), and/or renal insufficiency that, if not successfully treated, evolves to end-stage renal disease (ESRD) (1-3). Renal biopsy shows nodular glomerulosclerosis, resembling diabetic glomerulosclerosis, and deposits of nonamyloid immunoglobulin LCs in glomerular and tubular basement membranes on immunofluorescence (IF) (1-3).

The treatment options for LCDD are limited and the optimal management remains controversial. Until now, chemotherapy with steroids and melphalan has shown modest results (6). A combination of high-dose melphalan and autologous stem cell transplantation (ASCT) has been used in some patients and has led to an improvement of renal function (7), but high mortality rates and adverse effects limit the use of this regimen (8). Recently, the combined administration of bortezomib and dexamethasone has shown clinical activity in MM patients, even those with ESRD who are undergoing dialysis (9, 10). Furthermore, promising results have been reported in LCDD patients (11-13). Bortezomib, a reversible proteasome inhibitor, leads to apoptosis of the malignant plasma cells that show abnormal proliferation and consequently, reduces LC burden (9, 10). However, there have not been many reports regarding LCDD patients treated by bortezomib. In addition, the efficacy and safety of bortezomib in elderly patients have not been sufficiently confirmed.

We herein report a case of LCDD in an elderly patient successfully treated with bortezomib combined with dex-

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amethasone (BD therapy). In addition, 15 previously reported cases treated by BD therapy, as the present case, are reviewed, and the rarity and significance of the present case are highlighted.

Case Report

An 83-year-old woman was admitted to our hospital at the beginning of July 2013 with NS. Her medical history included hypertension (HT) and longstanding type 2 diabetes mellitus (DM). DM was first noted in 1992 and medication was started from 2002. Proteinuria had not been detected and her kidney function had been normal. In addition, there was no evidence of diabetic retinopathy. She did not have a history of alcohol consumption, smoking, or surgery. Her family medical history was unremarkable. Her first subjective symptom was lower extremity edema at the end of June 2013, and urinalysis in another hospital showed marked elevation of proteinuria (13.1 g/g Cr). She was then diagnosed with NS and her kidney function had been normal. In addition, there were no evidences of diabetic retinopathy. She did not have a history of alcohol consumption, smoking, or surgery. Her family medical history was unremarkable. Her first subjective symptom was lower extremity edema at the end of June 2013, and urinalysis in another hospital showed marked elevation of proteinuria (13.1 g/g Cr). She was then diagnosed with NS and referred to our hospital for detailed examination.

On admission, her temperature was 36.8°C, her pulse rate was 72 beats per minute, and her blood pressure was 149/72 mmHg. The findings of a physical examination were unremarkable, except for severe limb edema. Her laboratory tests revealed the following results: white blood cell count, 6,700/µL; erythrocyte count, 393×10⁶/µL; hematocrit, 36.6%; platelet count, 29.0×10⁵/µL; total protein, 6.2 g/dL; albumin (Alb), 2.6 g/dL; blood urea nitrogen, 11.6 mg/dL; creatinine (Cr), 1.0 mg/dL; estimated glomerular filtration rate (eGFR), 40.3 mL/min; total cholesterol, 401 mg/dL; triglycerides, 322 mg/dL; hemoglobin A1c, 5.8%; C-reactive protein, 0.1 mg/dL; IgG, 1,410 mg/dL; IgA, 181 mg/dL; IgM, 85 mg/dL; C3, 104.1 mg/dL; C4, 41.8 mg/dL; and CH50, 48 U/mL. Her tests for antinuclear antibodies, cryoglobulins, and circulating immune complexes were negative. A 24-hour urine collection showed 4.8 g of protein. The urinary sediment contained 5-9 red blood cells per high-power field. The Cr clearance was 37.2 mL/min. An M-spike was detected on serum protein electrophoresis. Serum and urine immunoelectrophoresis (IEP) showed an M-bow of the IgG-κ type. Urinary Bence-Jones protein was not detected. A serum free light chain (FLC) assay revealed marked elevation of κ chains at 90.6 mg/L (3.3-19.4 mg/L), while λ chains were normal at 18.2 mg/L (5.7-26.3 mg/L), with an elevated κ:λ ratio of 4.98 (0.26-1.65). Bone marrow aspiration and biopsy revealed 3.8% plasma cells and normal cytogenetics. Immunohistostaining of the bone marrow showed that monoclonal plasma cells expressed κ chains and these monoclonal plasma cells were positive for VS38c, CD138, and CD56. The skeletal survey was negative for lytic lesions or pathologic fractures. Based on these findings, the patient was diagnosed as having MGUS.

On day 22 after admission, a renal biopsy (RBx) was performed to obtain a definitive diagnosis on which to base a treatment plan. A total of 11 glomeruli were available, 2 of which showed global sclerosis. Light microscopy (LM) findings showed periodic acid-Schiff (PAS)-positive subendothelial deposits and focal segmental glomerulosclerosis (Fig. 1A). The tubulointerstitial showed a mild degree of cellular infiltration, tubular dilatation, and fibrosis accompanied by tubular atrophy. Additionally, PAS-positive hyaline droplet degeneration was detected in tubular epithelial cells (TECs) (Fig. 1B). Congo red stain was negative. On IF, IgG was negative in the glomeruli (Fig. 2A) and tubules (Fig. 2D). Regarding LCs, positivity for κ was detected in the glomerular basement membrane (Fig. 2B), as well as in TECs (Fig. 2E). On the other hand, λ was negative (Fig. 2C, F). On electron microscopy (EM), electron-dense deposits (EDD) were not detected in the glomeruli. Furthermore, there was no evidence of crystal deposits in tubules that should be seen in light chain proximal tubulopathy with crystal formation (14). However, dense granules, lipid droplets, and disruption of the brush border were detected in proximal tubules (Fig. 3). Based on these pathological findings, the patient was diagnosed to have LCDD of κ type and her tubulointerstitial lesions were compatible with light

Figure 1. Light microscopy of a renal biopsy sample. (A) The glomerulus shows periodic acid-Schiff (PAS) positive subendothelial deposits and segmental mesangial glomerulosclerosis (Original magnification ×400). (B) Hyaline droplet degeneration (arrows) is detected in proximal tubular epithelial cells (Original magnification ×200).

![Image](image-url)
chain proximal tubulopathy without any crystal formation (14). These findings strongly supported a diagnosis of LCDD associated with MGUS.

To reduce the LC burden and attempt to preserve the renal function, chemotherapy was begun. In consideration of her advanced age, she was started on a new regimen of monthly chemotherapy with bortezomib (1.3 mg/m² intravenous bolus injection once monthly) and dexamethasone (20 mg on the days of bortezomib administration) under the guidance of a hematologist. After 13 cycles of the treatment, the patient remained in good condition (Fig. 4). The total free κ and the κ/λ ratio had decreased to 31.9 mg/L and 1.61, respectively, which correlated with the decrease in urinary protein from 10.7 to 0.15 g/gCr and an increase in the serum Alb level from 2.4 to 4.5 g/dL. Regarding the renal function, BD therapy did not affect her renal function. After 13 cycles of the treatment, serum Cr and eGFR were 1.1 mg/dL and 35.0 mL/min, respectively. In addition, her current serum Cr level remains within 1.1 mg/dL. Furthermore, the serum and urine IEP showed a disappearance of the M-bow of the IgG-κ type, thus fulfilling the criteria for complete remission (15). No adverse effects of bortezomib, including peripheral neuropathy, transient thrombocytopenia, or viral infection, were detected.

Discussion

For a conclusive diagnosis of LCDD, IF is therefore recognized to be an indispensable method. In previous reports, LCDD has been defined by mainly IF as deposits of clear monoclonal LCs (16-18). In the present case, IF showed only kappa positive findings in glomerulus. However, typical granular-powdery EDD were not apparent. In accordance with the previous report by Lin et al., our patient could thus be diagnosed to have “LCDD by IF only” (16). They reported four patients who had monoclonal LC staining by IF but no correspondingly EDD by EM. In addition, we did not identify nodular mesangial sclerosis, which is commonly detected on LM. However, the incidence of nodular lesion in patients with LCDD is reported to range from 31 to 74% (2, 16, 17), which indicates its absence does not exclude a diagnosis of LCDD. On the other hand, we identified segmental mesangial sclerosis and PAS-positive subendothelial deposits. In the previous report, the incidence of mesangial sclerosis without nodule formation was present in 5 of the 51 patients (8%) with LCDD (17), but subendothelial deposits are considered to be affected by longstanding
HT and DM rather than LCDD. Therefore, we diagnosed this patient to have LCDD associated with MGUS. Furthermore, the fact that the improvement of proteinuria was associated with a significant reduction of serum free LC by BD therapy supports our diagnosis. Concerning the tubulointerstitium, at first we assumed the deposition of LCs in TECs because of the positivity for κ on IF. However, there was no evidence of EDD or crystals on EM. In addition, the deposition of LCs in TECs is reported to be negative by PAS staining (14). Therefore, κ positive findings in TECs are considered to be incompatible with the deposition in LCDD. Conversely, we considered the excess κ LCs which passed through the damaged glomerulus to have been reabsorbed by the proximal TECs, which caused focal κ positive findings in TECs, PAS-positive hyaline droplet of degeneration in proximal tubules, and nonspecific injury to the renal proximal TECs.

In general, LCDD is recognized to be rare. Previously, Nasr et al. indicated the biopsy incidence of LCDD to be 0.5% (17). In their reports, 51 patients with a diagnosis of LCDD were identified based on a retrospective review of all renal biopsies (n=10,481) at the Mayo Clinic from 1992 to 2011 (17). Additionally, their mean age was reported to be 55 years (17). Similarly, Pozzi et al. showed the mean age of the LCDD patients to be 58 years of age in their multicenter study (18). They mentioned that the frequency of diagnosing LCDD was higher in middle-aged adults than in the elderly population (17, 18). Therefore, we consider that the case of an elderly patient, especially over 80 years of age, as in the present case, is very rare, although physicians might not perform RBx in elderly patients.

With regard to the outcome, the median survival in patients with LCDD is about 4 years (5, 16). The largest series published so far has reported a median follow-up of 27 months; 57% of patients developed ESRD and 59% of patients died (18). In addition, Nasr et al. also reported the outcomes of LCDD patients. In their report, 15 of the 48 patients (31%) with LCDD died. The mean time from biopsy to death in those who died was 20 months. Furthermore, 17 (38%) patients progressed to ESRD in 6 months on average (17). Therefore, these reports remind us that LCDD has a poor prognosis. Concerning prognostic factors, the patient’s age, the degree of renal damage, the presence of MM, and the extrarenal deposition of LC were reported to be essential (16-18). Although the present patient had NS and an advanced age, the performance status and activities of daily living were relatively well-maintained, and she did not show dementia or appetite loss and was not bedridden. Therefore, we considered that the patient should be treated with appropriate therapy to prevent the progression to ESRD or death.

Next, we consider BD therapy. Besides directly reducing LC burden, there are several reports to indicate that bortezomib may also have a renoprotective effect (11-13). In the setting of LCDD, nuclear factor kappa B (NF-κB), activated in proximal tubules and glomerular mesangial cells, plays a pivotal role. NF-κB is known to induce platelet-derived growth factor-β and tumor growth factor-β (TGF-β), thus leading to cellular proliferation and collagen production. Bortezomib has been suggested to inhibit NF-κB, thereby decreasing TGF-β levels and collagen production, eventually preventing glomerulosclerosis and renal dysfunction (11-13). Furthermore, several case reports have already shown that bortezomib stabilizes the renal function in patients with LCDD without serious adverse effects (19-24). Based on these data and those obtained from reports, it was decided to administer BD therapy to this elderly patient.

To the best of our knowledge, 15 LCDD patients treated
by BD therapy have been reported in the literature. Table shows the clinical features of the 15 previously reported cases and the present case. These patients’ ages ranged from 36 to 83 years. The present case was the oldest, and no other patients were over 70 years old. Ten patients received prior therapy, including ASCT. MM was seen in 8 patients. These patients had more monoclonal immunoglobulin LC and exhibited more severe clinical findings compared to MGUS patients such as the present case. LC isotype was more frequently κ than λ, compatible with previous reviews (17, 18). Serum FLCs were elevated in all patients with available patient data, which caused abnormal k/λ ratios. Renal impairment was seen in all patients and it was accompanied with moderate to severe proteinuria. With regard to the regimen of BD therapy, most physicians adopted the standard regimen: a combination of bortezomib 1.3 mg/m² on days 1, 4, 8, 11 and dexamethasone 40 mg on days 1-4 every 21 days. Weekly: weekly regimen: combination of bortezomib 1.3 mg/m² once weekly and dexamethasone 40 mg on days 1-4 every 5 days. Modified: modified regimen: combination of bortezomib (1.6 mg/m² on days 1, 8, 15), cyclophosphamide (500 mg/m² on day 1), dexamethasone (20 mg on the days of and after bortezomib administration), and thalidomide (100 mg daily). Monthly: monthly regimen: combination of bortezomib 1.3 mg/m² once monthly and dexamethasone 20 mg on the days of bortezomib administration. FLC: free light-chain, sCr: serum creatinine, ESRD: end stage renal disease, UP: urinary protein, PN: peripheral neuropathy, PR: partial remission: >50% decrease of the involved monoclonal paraprotein, CR: complete remission: normalization of the involved monoclonal paraprotein and serum free light chain k/λ ratio.

In conclusion, based on a review of 16 cases, including the present case, bortezomib-based chemotherapy appears to be a convincing strategy for the treatment of LCDD. Although a modified regimen of bortezomib-based chemotherapy is feasible for elderly patients with LCDD, it is necessary to accumulate a larger number of similar cases to establish the optimal therapeutic strategies.

The authors state that they have no Conflict of Interest (COI).

References


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<th>Ref</th>
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Abbreviations: Ref: reference, y: years, M: male, F: female, Tx: therapy, VAD: dexamethasone and dexamethasone, CYP: cyclophosphamide, ASCT: autologous stem cell transplantation, PE: plasma exchange, Rit: rituximab, PCs: plasma cells, BM: bone marrow, LC: light-chain, PCD: plasma cell dyscrasia, MM: multiple myeloma, MGUS: monoclonal gammopathy of undetermined significance, BD: bortezomib and dexamethasone therapy, Standard: standard regimen: combination of bortezomib 1.3 mg/m² on days 1, 4, 8, 11 and dexamethasone 40 mg on days 1-4 every 21 days, Weekly: weekly regimen: combination of bortezomib 1.3 mg/m² once weekly and dexamethasone 40 mg on days 1-4 every 5 days, Modified: modified regimen: combination of bortezomib 1.6 mg/m² on days 1, 8, 15), cyclophosphamide (500 mg/m² on day 1), dexamethasone (20 mg on the days of and after bortezomib administration), and thalidomide (100 mg daily), Monthly: monthly regimen: combination of bortezomib 1.3 mg/m² once monthly and dexamethasone 20 mg on the days of bortezomib administration, FLC: free light-chain, sCr: serum creatinine, ESRD: end stage renal disease, UP: urinary protein, PN: peripheral neuropathy, PR: partial remission: >50% decrease of the involved monoclonal paraprotein, CR: complete remission: normalization of the involved monoclonal paraprotein and serum free light chain k/λ ratio. No: no response, NA: not available.


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