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【 CASE REPORT 】

Lenalidomide as a Beneficial Treatment Option for Renal Impairment Caused by Light Chain Deposition Disease

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Abstract:

Light chain deposition disease (LCDD) is a rare systemic disorder caused by the deposition of light chain immunoglobulins, which often results in renal impairment associated with either nephrotic syndrome or asymptomatic proteinuria. B-cell neoplasms, such as multiple myeloma and lymphoproliferative disorders, are well-known underlying diseases in LCDD. Some chemotherapy regimens have been reported, but both evidence-based treatment and management for LCDD have yet to be established. We herein report three cases of LCDD treated with lenalidomide-based therapy, resulting in hematologic responses accompanied by a significant reduction in proteinuria and improvement in the renal function. We recommend lenalidomide-based therapy for renal impairment caused by LCDD.

Key words: light chain deposition disease, lenalidomide, nephrotic syndrome

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Introduction

Light chain deposition disease (LCDD) is characterized by the deposition of monoclonal light chains in organs such as the kidney, liver, heart, lung and gastrointestinal tract (1, 2). Most patients with renal impairment caused by LCDD develop nephrotic syndrome or asymptomatic proteinuria with microhematuria and hypertension (1, 2). The reduction of serum monoclonal light chains, which contributes to the improvement in the renal function, is valuable for the therapeutic evaluation of patients with renal impairment caused by LCDD (1). In the absence of medical treatment, such impairment is often at risk of progression to chronic kidney disease (1, 2).

According to the World Health Organization classification of tumors of hematopoietic and lymphoid tissues, LCDD is categorized as "a monoclonal deposition disease" (3). The detection of monoclonal light chains deposited in the organs indicates underlying plasma cell dyscrasia or lymphoproliferative disease (1-3). The monoclonal light chains in LCDD, which are mainly κ-type light chains, are deposited in the basement membranes of cells in the kidneys, and the characteristic findings on a histological examination show the deposition of monoclonal light chains in the renal glomerular basement membrane (GBM) and tubular basement membrane (TBM) (4, 5). The most common causes of death are infection, ischemic heart disease, end-stage renal disease, congestive cardiac failure, cerebrovascular accident, gastrointestinal hemorrhage, multiple myeloma (MM) and AL amyloidosis (1, 6, 7). However, a standard treatment approach to LCDD has yet to be established. Lenalidomide, an immunomodulatory drug, significantly improves the clinical response and overall survival of patients with MM (8-10).

We herein report a case series of LCDD with developing renal impairment associated with nephrotic syndrome that

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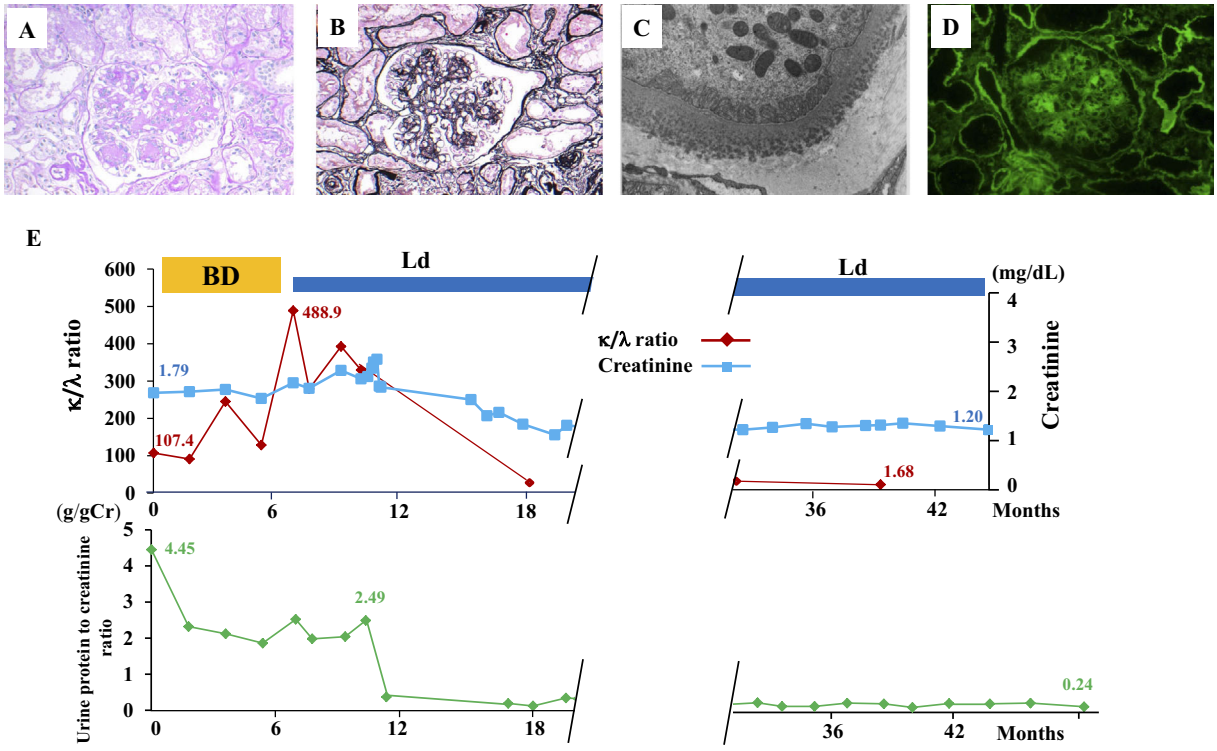

Figure 1. **Histological findings of LCDD-induced renal impairment revealed by a kidney biopsy. (A) Original magnification, periodic acid-Schiff stain ×200. (B) Original magnification, periodic acid methenamine silver stain ×200. (C) Original magnification, electron microscope ×3,000. (D) Original magnification, immunohistochemical stain for κ light chain ×200. (E) Clinical course. After lenalidomide-based therapy for bortezomib-resistant LCDD, the progressive renal impairment was improved with a good hematological response. The patient's κ/λ ratio was significantly decreased from 392.9 to 0.87, and his creatinine level remained normal. LCDD: light chain deposition disease, BD: bortezomib (2.3 mg, twice weekly) and dexamethasone (20 mg, twice weekly), Ld: lenalidomide (10 mg daily, on Days 1 through 21 of each 28-day cycle) and dexamethasone (20 mg once weekly)**

was successfully treated with a lenalidomide-based therapy. In all of the present cases, lenalidomide-based therapy improved the renal impairment by decreasing the high levels of serum monoclonal light chains, resulting in a marked reduction in proteinuria. The use of bortezomib and lenalidomide for LCDD was approved by the ethics committee of Fukushima Medical University.

Case Reports

Case 1

A 69-year-old man visited our hospital with generalized weakness and renal impairment. At the presentation, a physical examination revealed pitting edema of the bilateral lower extremities. He had a temperature of 36.2°C, a pulse rate of 62/min, a respiration rate of 14/min and a blood pressure of 164/98 mmHg. Laboratory findings were as follows: white blood cell count 9,700 cells/mm^3, hemoglobin level 12.0 g/L, platelet count 242×10^9/L, serum albumin 4.4 g/dL, total protein 8.8 g/dL, urea nitrogen 30.6 mg/dL and serum creatinine 1.79 mg/dL. The urine protein-to-creatinine ratio was 4.45 g/gCr, and ultrasonography showed severe atrophy of the bilateral kidneys. The patient's IgG serum level was 2,169 mg/dL, with an IgA level of 35 mg/dL and an IgM level of 25 mg/dL, and his κ/λ ratio was 107.4. His serum free κ light chain level was 131.0 mg/L. Immunoelectrophoresis identified abnormal serum κ-type IgG immunoglobulin and κ-type Bence Jones protein.

Bone marrow aspiration revealed 4.6% atypical plasma cells, resulting in a diagnosis of IgG-κ monoclonal gammopathy of undetermined significance (MGUS). A histological examination showed glomeruli with typical nodular lesions resembling those in diabetic glomerulosclerosis. Thickening of the TBM and slight tubular atrophy were also observed (Fig. 1A and B). Congo red staining was negative (data not shown). An electron microscope analysis revealed continuous granular subendothelial dense deposits along the GBM, as well as electron dense deposits on the outer aspect of the TBM (Fig. 1C). Immunofluorescence staining with anti-κ light chain antibody demonstrated positive staining in glomerular nodules, GBM, and TBM (Fig. 1D).

Treatment was started with bortezomib (2.3 mg, twice weekly) and dexamethasone (20 mg, twice weekly), and his renal function was temporarily improved (Fig. 1E). After 6 cycles of the bortezomib-based regimen, therapy with

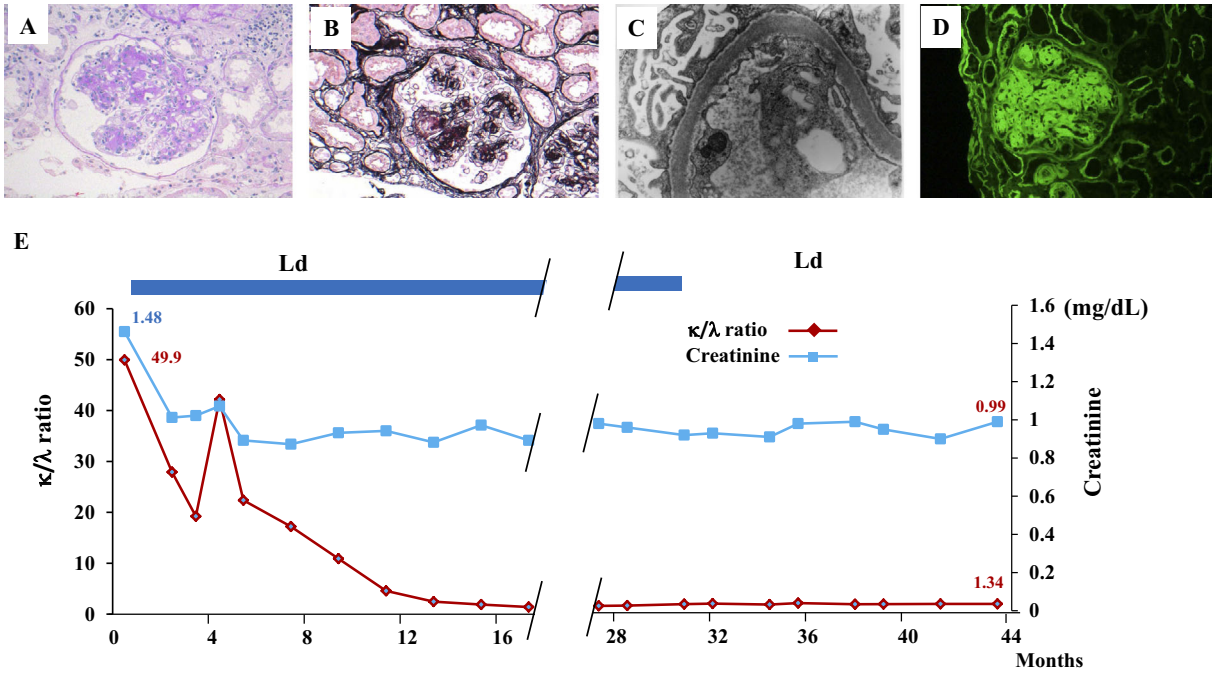

Figure 2. **Histological findings of LCDD-induced renal impairment revealed by a kidney biopsy. (A) Original magnification, periodic acid-Schiff stain ×200. (B) Original magnification, periodic acid methenamine silver stain ×200. (C) Original magnification, electron microscope ×3,000. (D) Original magnification, immunohistochemical stain for κ light chain ×200. (E) Clinical course. After short-term low-dose treatment with lenalidomide, the renal impairment and proteinuria caused by LCDD was improved, the κ/λ ratio was markedly decreased, and the creatinine level remained normal. LCDD: light chain deposition disease, Ld: lenalidomide (25 mg daily, on Days 1 through 21 of each 28-day cycle) and dexamethasone (20 mg once weekly)**

reduced-lenalidomide (10 mg daily, on Days 1 through 21 of each 28-day cycle) in combination with dexamethasone (20 mg, once weekly) (Ld therapy) was initiated because his renal function was exacerbated, as evidenced by an elevation of his creatine levels and the urine protein to creatinine ratio in association with an increase in the κ/λ ratio. The patient's k/l ratio dramatically decreased after the first two courses of Ld therapy, although his renal function was not improved. No other promising treatment strategy for LCDD was available at that time. We therefore continued Ld therapy. Subsequently, the continuation of Ld therapy remarkably decreased his urine protein to creatinine (g/gCr) ratio and the patient's renal insufficiency was improved with a good hematological response. In addition, his κ/λ ratio significantly decreased from 488.96 to 1.68, and his creatinine level remained normal (Fig. 1E).

Case 2

A 59-year-old man was referred to our hospital for an evaluation of his renal impairment and severe edema of the bilateral lower legs. He had no relevant medical history. On an examination, he had a temperature of 36.7°C, a pulse rate of 103/min, a respiration rate of 18/min and a blood pressure of 165/102 mmHg. Laboratory findings were as follows: white blood cell count 7,900 cells/mm^3, hemoglobin level 13.6 g/L, platelet count 308×10^9/L, serum albumin 2.4 g/dL, total protein 5.2 g/dL, urea nitrogen 17 mg/dL and serum creatinine 1.48 mg/dL. Protein and occult blood were observed in his urine. In addition, his urinary protein excretion was 4.0 g daily, and his urine protein-to-creatinine ratio was 2.50 g/gCr. His IgG serum level was 933 mg/dL, with an IgA level of 59 mg/dL and an IgM level of 47 mg/dL. Therefore, a clinical diagnosis of nephrotic syndrome was made.

Immunoelectrophoresis identified abnormal serum κ-type IgG immunoglobulin and urinary κ-type Bence Jones protein. A significant elevation of the serum κ light chain was detected in comparison to that of the λ chain, and the patient's κ/λ ratio was 49.94. His serum free κ light chain level was 844.0 mg/L. Bone marrow aspiration revealed approximately 6.0% atypical plasma cells, resulting in our diagnosis of IgG-MGUS.

To determine the cause of the nephrotic syndrome, a renal biopsy was performed. Light microscopy showed diffuse mesangial cell proliferation and an increase in mesangial matrix that contained nodular lesions (Fig. 2A). Periodic acid methenamine silver staining showed global mesangial expansion with accumulation of mesangial matrix and a double contour of the GBM (Fig. 2B). The tubulointerstitium exhibited lymphocyte infiltration, fibrosis and moderate tubular atrophy (Fig. 2A), and Congo red staining was negative (data not shown). An electron microscope analysis

showed band-like subendothelial electron-dense deposits along the GBM, indicating fine granular subendothelial dense deposits along the GBM (Fig. 2C). Immunofluorescence microscopy was strongly positive for κ light chains along the GBM and TBM (Fig. 2D). Thus, a diagnosis of nephrotic syndrome caused by LCDD was made.

Treatment with dose-adjusted lenalidomide for the renal dysfunction caused by LCDD was started after obtaining the patient's informed consent. The treatment was reduced-lenalidomide (10 mg daily, on Days 1 through 21 of each 28-day cycle) and dexamethasone (20 mg, once weekly). After treatment with lenalidomide for 30 months, the patient's proteinuria disappeared, and his serum albumin level subsequently increased from 2.4 g/dL to 3.8 g/dL. His κ/λ ratio significantly decreased from 49.94 to 0.89, and his serum creatinine improved from 1.27 mg/dL to 0.99 mg/dL. Throughout the follow-up period, his creatinine level remained normal (Fig. 2E). For economic reasons, he refused to continue treatment with lenalidomide and high-dose melphalan (HDM) and declined autologous stem cell transplantation (ASCT).

Case 3

A 60-year-old woman presented with generalized weakness that had started 3 months earlier. She had bilateral leg edema, proteinuria and hypertension. On an examination, she had a temperature of 37.0°C, a pulse rate of 65/min, a respiration rate of 14/min and a blood pressure of 180/60 mmHg. Bilateral pitting edema of the lower extremities was noted. The laboratory findings were as follows: white blood cell count 4,600 cells/mm^3, hemoglobin level 10.6 g/L, platelet count 227×10^9/L, serum albumin 3.8 g/dL, total protein 6.7 g/dL, urea nitrogen 19 mg/dL and serum creatinine 0.79 mg/dL (eGFR 58 mL/min). The patient's IgG serum level was 1,195 mg/dL, with an IgA level of 149 mg/dL and an IgM level of 86 mg/dL, and no monoclonality was observed. Her urine protein-to-creatinine ratio was 7.78 g/gCr, and κ-type Bence Jones protein was detected by immunoelectrophoresis.

Bone marrow aspiration showed a slight increase in the plasma cells (4.2% of nucleated cells). A serum free light chain analysis showed increased free κ light chain (676.0 mg/L), reduced free λ light chain (16.9 mg/L) and an abnormal ratio of κ/λ light chain (40.0). A percutaneous renal biopsy showed that the glomeruli were enlarged with global mesangial proliferation and segmental endocapillary proliferation with double contour, showing typical nodular lesions (Fig. 3A and B). Furthermore, the infiltration of mesangial cells and marked thickening of the GBM were noted on sclerotic glomeruli, along with nodular glomerular lesions. In addition, the lesions were diffusely distributed on the loop and arteriolar walls, and infiltrating foamy cells were noted in the expansion lesions with marked thickening of the GBM (Fig. 3A and B). Congo red staining was negative (data not shown), and an electron microscope analysis revealed fine granular dense deposits along the subendothelial space of the GBM (Fig. 3C). Immunofluorescence microscopy showed strong staining for κ light chains along the GBM (Fig. 3D). The clinical and histological findings confirmed the diagnosis of κ-type LCDD with MGUS.

Treatment with lenalidomide, which required dose-adjustment was initiated. The patient received induction with four cycles of lenalidomide (15 mg daily, on Days 1 through 21 of each 28-day cycle) and dexamethasone (40 mg once weekly) followed by HDM (140 mg/m^2) plus ASCT. In addition, she received low-dose lenalidomide maintenance therapy (10 mg daily, on Days 1 through 21 of each 28-day cycle) after HDM followed by ASCT, resulting in a good hematological response. Throughout the follow-up period, her κ/λ ratio significantly decreased from 40.0 to 1.07, and the patient's creatinine level remained normal (Fig. 3E).

Discussion

LCDD is a rare systemic disease associated with renal, cardiac, pulmonary, hepatic and gastrointestinal involvement caused by the deposition of monoclonal light chains (1, 2). Monoclonal immunoglobulin deposition disease (MIDD) is characterized by the deposition of monoclonal immunoglobulin molecules in the renal GBM and TBM and is one of three types defined by the composition of the deposits: LCDD, light and heavy chain deposition disease, and heavy chain deposition disease (4, 11). Monoclonal gammopathy of renal significance (MGRS) was first described by the International Kidney Monoclonal Gammopathy Research Group and is defined as renal impairment due to monoclonal immunoglobulin deposition (most commonly IgG3κ) produced by underlying B-cell or plasma-cell clones (12, 13). One type of MGRS is characterized by non-organized electro-dense granular deposits in MIDD, which results in a proliferative or membranoproliferative pattern of kidney injury (12).

The histological characteristic features of LCDD are nodular glomerulosclerosis, thickening of the GBM and/or TBM, or mesangial matrix increase (4, 5). In addition, nodular glomerulosclerosis is found in around 50% of nephrotic patients and 25% of non-nephrotic patients (14). Immunofluorescence and electron microscopy can reveal linear deposits of monoclonal light chains on the glomerular capillaries and nodules, as well as along Bowman's capsule and the TBM, resulting in cell proliferation and activation of specific genes responsible for collagen and tenascin production (1, 2, 15). Furthermore, electron microscopy is clinically useful in demonstrating granular electron-dense deposits in the mesangium, as well as all renal basement membranes in LCDD (5, 15). In a study by Sayed et al., the median age at the diagnosis of LCDD was 56 years (range, 29-78 years), and the male/female ratio was 2.3:1 (1). In the same study, the median renal survival from the diagnosis of LCDD was 5.4 years, and the median estimated patient survival was 14.0 years (1). In addition, some patients have been reported to obtain a long-term survival with kidney

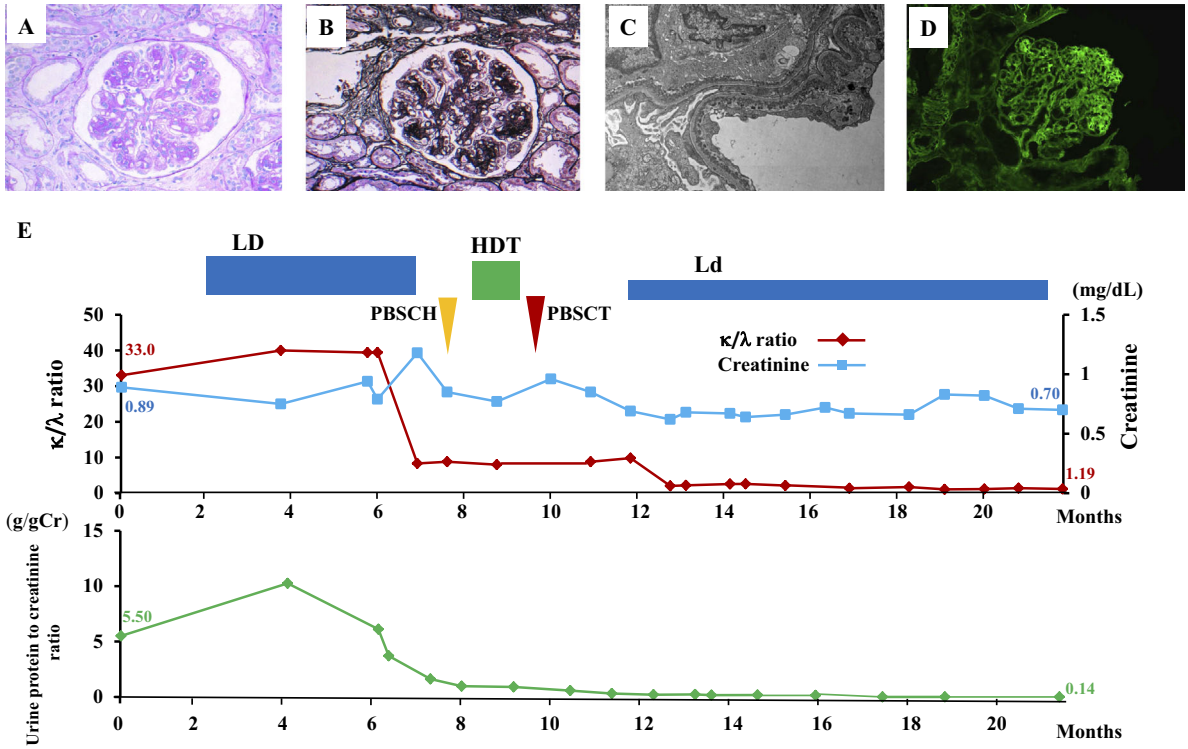

Figure 3. **Histological findings of LCDD-induced renal impairment revealed by a kidney biopsy. (A) Original magnification, periodic acid-Schiff stain ×200. (B) Original magnification, periodic acid methenamine silver stain ×200. (C) Original magnification, electron microscope ×3,000. (D) Original magnification, immunohistochemical stain for κ light chain ×200. (E) Clinical course. After high-dose melphalan plus autologous stem cell transplantation, the patient received low-dose lenalidomide maintenance therapy (10 mg daily for three weeks). Throughout the follow-up period, her κ/λ ratio significantly decreased from 40.0 to 1.07, and her creatinine level remained normal. LCDD: light chain deposition disease, LD: lenalidomide (25 mg daily, on Days 1 through 21 of each 28-day cycle) and dexamethasone (40 mg once weekly), HDM: high-dose melphalan (140 mg/m^2), PBSCH: autologous peripheral blood stem cell harvest, PBSCT: autologous peripheral blood stem cell transplantation, Ld: lenalidomide (10 mg daily, on Days 1 through 21 of each 28-day cycle) and dexamethasone (20 mg once weekly)**

transplantation, but LCDD frequently recurs after kidney transplantation (16, 17). The treatment of renal failure caused by LCDD and recurrent LCDD after kidney transplantation is also required (1, 16, 17).

Lenalidomide, an immunomodulatory drug, has been shown to improve the outcomes of patients with newly-diagnosed, previously-treated or refractory MM (8-10). Lenalidomide has been shown to induce apoptosis of MM cells and inhibit angiogenesis and blocks the binding of MM cells to the bone marrow stromal cells (18, 19). In addition, the E 3 ligase protein cereblon has been identified as a therapeutically-important molecular target of lenalidomide (20). Lenalidomide is known to stimulate T and natural killer cells for MM cells, which produce cytokines such as interleukin-6, tumor necrosis factor-α, transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) mediated via the NF-κB pathway (21-23). The interaction of renal glomerular mesangial cells with monoclonal light chains has been shown to activate cytokines such as TGF-β and VEGF in combination with the high production of matrix and extracellular matrix proteins, which compose the glomerular lesions in LCDD (21-24). Interestingly, lenalidomide has been also shown to down-regulate the production of cytokines that include TGF-β by activated monocytes while simultaneously up-regulating IL-2 and interferon-γ production, which promotes the activation of T and natural killer cells (21-24). There are no prospective trials to guide the evidence-based treatment of LCDD with MM or MGUS; however, several treatment approaches for LCDD, such as chemotherapy and HDM with ASCT, have been reported (25). Bortezomib-based therapy has been attempted in patients with LCDD, with varied responses, and the reduction in the monoclonal light chains after treatment with bortezomib has been reported to result in the improvement in the renal function by inhibiting the progression of glomerulosclerosis with histological confirmation (26-28). However, in Case 1 of the present study, initial bortezomib-based therapy lacked a sufficient effect on renal impairment, whereas lenalidomide-based therapy resulted in significant improvement, indicating the clinical benefits of

Table. **Reported Cases with LCDD Treated with Lenalidomide-based Regimens.**

Ref No.	Age (years)	Sex	MM	LC type	Clinical feature	Regimens	Hematological response	Renal response	Follow-up period (months)
6	69	F	-	λ	heart skeletal muscle amyloidosis	lenalidomide/ predonine	ND	ND	1 sudden death
29	78	M	+	κ	hepatic artery, kidney	predonine/ melphalan/ lenalidomide	PR	ND	3
30	61	M	-	κ	kidney, GI tract, heart, liver	lenalidomide/ dexamethasone	PR	improved	30
31	69	M	-	λ	kidney	lenalidomide/ cyclophosphamide/ dexamethasone	VGPR	improved	12
Case 1	69	M	-	κ	kidney	lenalidomide/ dexamethasone	VGPR	improved	44
Case 2	59	M	-	κ	kidney	lenalidomide/ dexamethasone	VGPR	improved	44
Case 3	60	F	-	κ	kidney	lenalidomide/ dexamethasone ASCT	VGPR	improved	24

LCDD: Light chain deposition disease, MM: multiple myeloma, LC: light chain, F: females, M: males, GI: gastrointestinal, ASCT: autologous peripheralblood stem cell transplantation, ND: not detectable, PR: partial response, VGPR: very good partial response

lenalidomide on bortezomib-refractory LCDD with MGUS (Fig. 1E).

In our exploration of the reported literature, we identified four other cases of the beneficial effects of lenalidomide on various organ disorders caused by LCDD (Table). It has been reported that a very rare case of severe ischemic cholangitis in a patient with LCDD, who received chemotherapy with melphalan, prednisone and lenalidomide, achieved prolonged a partial hematological response (29). Some investigators also reported the effects of lenalidomide on LCDD (30, 31). Dose-reduced lenalidomide has been administered to myeloma patients with various degrees of renal function without apparent toxicity (32, 33). In Cases 1 and 2 of the present study, low-dose treatment with lenalidomide significantly improved the renal impairment caused by LCDD (Fig. 1E). An LCDD patient who received HDM followed by ASCT reportedly showed a good partial response and subsequent improvement of LCDD-induced cardiac and renal dysfunction (34). However, toxicities of HDT in patients with renal impairment are frequent and severe; in such cases, the doses of melphalan should be decreased (35). In Case 3 of the present study, an attenuated dose of 140 mg/m^2 melphalan was used in order to reduce toxicity (Fig. 3E). Long-term maintenance with lenalidomide (10 mg daily, on Days 1 through 21 of each 28-day cycle) may be administered to all patients with MM despite concerns about the long-term safety, as the overall survival benefit has been widely established (36). Our Case 3 suggests that maintenance therapy with lenalidomide after HDM, followed by ASCT, may be a safe and beneficial option for LCDD.

Conclusion

In the present study, lenalidomide-based therapy demonstrated rapid hematologic responses, with adequate improvement of the impaired renal function and proteinuria, and decreases in the monoclonal light chain levels in patients with LCDD. We believe that lenalidomide-based therapy may be an effective option for the treatment of LCDD.

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

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