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Late Recurrence of Light Chain Deposition Disease after Kidney Transplantation Treated with Bortezomib: A Case Report

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ABSTRACT

Background: Light chain deposition disease (LCDD) recurs frequently after renal transplantation with variable presentation.

Case Report: We report the case of a 67-year-old Caucasian female with recurrence of LCDD after living-donor kidney transplantation. Bone marrow biopsy revealed kappa light chain-restricted population of plasma cells, and the patient met the criteria for multiple myeloma. Her renal function progressively worsened and she became dialysis dependent. She received 1 cycle of bortezomib along with intravenous dexamethasone. She was able to discontinue dialysis within 2 months, and at 1 year follow-up her renal function was stable.

Conclusion: Bortezomib has a role in the treatment of recurrent LCDD and multiple myeloma in kidney transplant patients. As opposed to traditional regimens, a short course may be beneficial.

INTRODUCTION

Monoclonal immunoglobulin (Ig) deposition disease (MIDD) is a systemic disorder characterized by tissue deposition of monoclonal light and/or heavy chains in various organs. Renal involvement is usually universal, although multiple organ systems, including the heart, liver, and peripheral nerves, may be affected.[1] MIDD presents as 3 major types, depending on the composition of the monoclonal paraprotein. Light chain deposition disease (LCDD) is the most common variety and comprises 75%-80% of cases of MIDD. Bone marrow involvement in LCDD is common, and the criteria for multiple myeloma (MM) are met in 40%-50% of cases.

LCDD occurs most frequently in older men, and the average age at presentation is 55-60 years. Patients usually present with proteinuria, microscopic hematuria, hypertension, and variable degrees of renal insufficiency.[2-4] Nephrotic-range proteinuria is common, but full-blown nephrotic syndrome occurs only in one-quarter of patients.[2]

The hallmark of LCDD on renal biopsy is nodular sclerosing glomerulopathy with variable thickening of the glomerular basement membranes (GBMs), tubular basement membranes (TBMs), and vascular basement membranes with brightly eosinophilic and strongly periodic acid-Schiff-positive material. Immunofluorescence is characteristic and shows intense (usually >2+) diffuse linear staining of renal basement membranes throughout all compartments of the kidney. Electron microscopy shows amorphous, nonfibrillar, finely granular, punctuate, highly electron-dense deposits.[2,5]

LCDD with renal manifestations, if untreated, may lead to end stage renal disease (ESRD).[6,7] In a series of 63 patients with LCDD, the median time to ESRD was 2.7 years, and patient survival was 66% at 1 year and 31% at 8 years.[3] More recent European data from 13 national registries consisting of 159,637 patients found that the incidence of renal replacement therapy (RRT) (adjusted for age and sex) because of LCDD or MM increased 3.6-fold in 2000-2005 compared to

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1985-1990. The median patient survival on RRT for MM and LCDD was 0.91 years, compared with 4.6 years for patients without MM. Patients who underwent renal transplantation did considerably better, with mean patient survival of 9.6 years.[8] In a report from the Mayo Clinic, 22 of 56 (39%) patients with MIDD progressed to ESRD during a median follow-up of 25 months (range 1-140 months).[9]

Treatment options for LCDD are limited and have shown mixed results. High doses of melphalan combined with autologous stem cell transplantation have been reported to produce significant and sustained improvement in renal function.[10,11] Chemotherapy with vincristine, doxorubicin, and dexamethasone has been used with limited success.[5] A case report suggested a possible role for rituximab in preventing or delaying LCDD recurrence in renal allograft.[12] Bortezomib, a reversible proteasome inhibitor, has shown some promise in reversing renal failure in patients with MM.[13-15] In a case series, 4 patients experienced improvement in hematological profile and renal function after receiving bortezomib.[16]

Although the long-term benefit of kidney transplantation in patients with LCDD has not been well established, transplant centers continue to perform kidney transplantation in this subgroup of patients. LCDD frequently recurs after kidney transplantation; however, only a few cases have been reported. More than 60% of recurrences are diagnosed within 5-50 months after transplantation.[17,18] Leung et al[17] retrospectively reviewed outcomes of 7 patients who underwent kidney transplantation for LCDD at the Mayo Clinic. Five of 7 (71%) patients developed recurrence at a median of 33 months (range 2-45 months). Four of 5 patients died and 1 remained on dialysis. Only 1 patient remained recurrence free at 13 years with normal renal function. Kaposztas et al[19] reported 1 case of early recurrence (within 2 weeks of transplantation) of LCDD that responded to bortezomib with discontinuation of dialysis and improvement in renal function.

We present the case of a patient who developed recurrence of LCDD several years after kidney transplantation, leading to allograft dysfunction requiring RRT. The patient had a significant improvement in her renal function after receiving bortezomib and was able to discontinue dialysis.

CASE REPORT

A 67-year-old Caucasian female with history of type 2 diabetes mellitus and hypertension was evaluated by her primary care physician for sudden onset of generalized swelling in June 2000. Initial testing revealed nephrotic-range proteinuria with mild renal insufficiency. The patient was subsequently referred to a nephrologist, and a kidney biopsy revealed kappa LCDD. Further testing, including serum protein electrophoresis (SPEP), showed no paraprotein, and immunofixation revealed no monoclonal band. Bone marrow biopsy showed increased plasma cells (7%) but did not meet the criteria for MM. Her renal function deteriorated gradually and she progressed to ESRD over the next 4 years. She started hemodialysis in 2004.

She underwent evaluation for kidney transplantation, and a bone marrow biopsy was repeated as part of the pretransplant workup. This biopsy again failed to show any evidence of plasma cell dyscrasia. She subsequently underwent living-unrelated-donor kidney transplantation in March 2005. Her induction consisted of intravenous (IV) Solu-Medrol and rabbit thymoglobulin (4.5 mg/kg in 3 divided dosages). She had immediate allograft function without the need for RRT. She was started on tacrolimus, mycophenolate mofetil, and prednisone for maintenance immunosuppression. Prednisone was tapered to 5 mg daily within 6 months. Her creatinine stabilized between 0.8-1.0 mg/dL. Her tacrolimus trough was maintained at 5-7 ng/mL after the first 12 months.

Her renal function remained stable during the first 6 years following transplantation. She continued immunosuppression without any significant side effects. Routine laboratory studies performed in March 2011 before her annual visit showed a creatinine level of 1.8 mg/dL. She was also found to have nephrotic-range proteinuria (9.5 g/g) on spot protein to creatinine (P/C) ratio, whereas previously her P/C ratio was $<$0.1 g/g. Hemoglobin of 9.3 g/dL indicated anemia, but other electrolytes were within normal range. She was promptly evaluated. Other than mild swelling of her lower extremities, she did not have any complaints. A 24-hour urine collection confirmed the degree of proteinuria. She underwent a kidney biopsy for diagnostic purposes.

Kidney biopsy showed marked nodular mesangial expansion with eosinophilic staining of GBMs by light microscopy (Figure 1). The GBMs were prominent and showed segmental splitting without holes, spikes, or corrugation. No fractured-appearing casts were seen. Congo red stain was negative for amyloid. Minimal lymphocytic interstitial infiltrate and no tubulitis or endothelialitis were seen. Also evident were 1+ smudgy staining of the mesangium, 1-2+ pseudolinear staining of GBMs, and 2-3+ pseudolinear TBM staining for kappa light chain by immunofluorescence (Figure 2). The staining for IgG, IgM, IgA, polyvalent antisera, and lambda was negative. A C4d stain was negative. Electron microscopy revealed widespread finely granular and amorphous deposits along the inner aspect of the GBMs and along the outer aspect of the TBMs (Figure 3). No immune complexes were seen by electron microscopy.

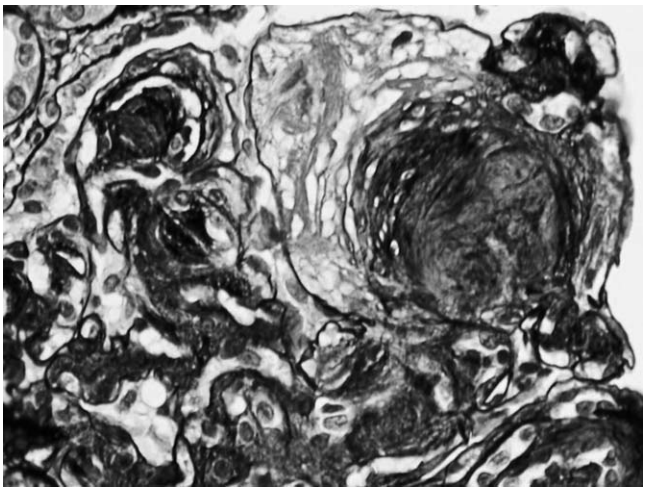

Figure 1. Nodular mesangial expansion with eosinophilic staining of glomerular basement membranes by light microscopy.

A diagnosis of recurrent LCDD was made based on the biopsy findings. The patient was immediately hospitalized for further evaluation. Initial investigations showed normal SPEP, and immunofixation revealed no monoclonal bands. Urine protein electrophoresis confirmed albumin as the primary protein (80%) along with the absence of a paraprotein band. Lambda free light chain was 0.56 mg/dL, and kappa free light chain was 106.08 mg/dL. Serum kappa/lambda free light chain ratio was 192.4 (normal, 1.5-2.0). Oncology was consulted, and bone marrow biopsy showed kappa light chain–restricted population of plasma cells with coexpression of CD38/CD56. No B-cell clonality or T-cell aberrancy was observed. Findings were consistent with a plasma cell dyscrasia, and the patient met the criteria for MM.

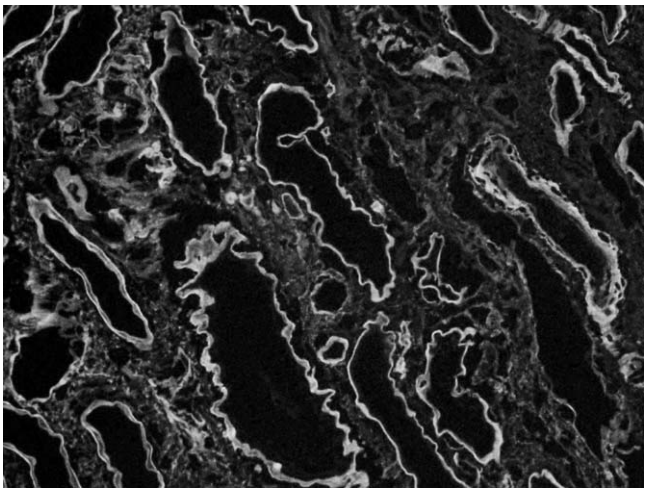

Figure 2. Tubular basement membrane staining for kappa light chain by immunofluorescence.

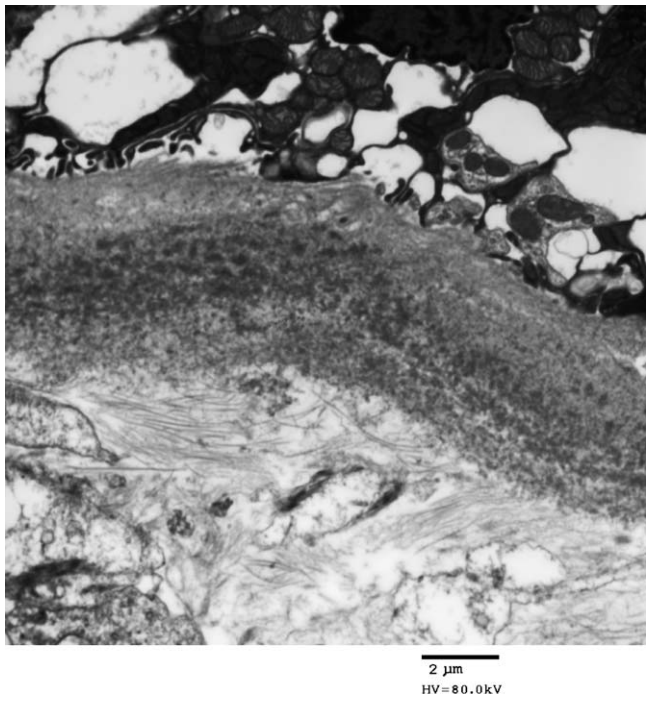

Figure 3. Finely granular and amorphous deposits on the inner aspect of glomerular basement membranes by electron microscopy.

The patient had a prolonged hospital course during which her renal function worsened progressively. Her immunosuppression was decreased, and mycophenolate mofetil was discontinued. She initially received 5 cycles of plasmapheresis without any improvement in renal function. She eventually required RRT 3 times per week for volume overload and uremia. She then received 1 cycle of bortezomib (1.3 mg/m^2 IV) along with IV dexamethasone. She received 4 doses of bortezomib on days 1, 4, 8, and 11. The patient showed no immediate clinical response to the treatment and remained dialysis dependent. She was discharged to a rehabilitation center because of significant debility and deconditioning. Her renal function was closely monitored while she remained on dialysis. She gradually exhibited signs of renal recovery after 2 months of dialysis. Dialysis was held when her urine output improved ($>$1 L/day), and her creatinine eventually settled between 1.5-1.7 mg/dL.

The patient was followed by the oncology department on an outpatient basis, and a second cycle of bortezomib was initiated after discussion with the patient. However, she received only 2 doses of bortezomib before developing neurological side effects, including changes in mental status and confusion, and severe peripheral neuropathy that limited further use of bortezomib. However, her renal

function remained stable, and her proteinuria gradually improved.

At 1-year follow up, the patient's creatinine was 1.9 mg/dL and proteinuria was <2 g/d. Her kappa free light chain level was 17.85 mg/dL, and her lambda free light chain level was 9.3 mg/dL. Her serum kappa/lambda ratio was 1.9 and her hemoglobin had improved to 11.4 g/dL. A follow-up bone marrow biopsy was offered; however, the patient refused to undergo the procedure.

DISCUSSION

Treatment options for LCDD remain limited. Management is particularly challenging for patients with recurrence after kidney transplantation. The general recommendation is that patients with ESRD should not undergo transplantation unless their synthesis of monoclonal protein has been controlled through effective therapy.

Conventional chemotherapy may be complicated for recurrent LCDD after transplantation because of frequent pancytopenia associated with immunosuppressive therapy. Leung et al[17]described LCDD recurrences in 2 of 3 patients who received low-dose melphalan and prednisone posttransplantation. One study attempted simultaneous kidney and bone marrow grafting from human antigen-identical siblings following nonmyeloablative conditioning.[20] All 6 patients accepted their kidney grafts and remained off immunosuppression for 1.3 to >7 years. The investigators concluded that the regimen of combined kidney and bone marrow transplantation achieved renal allograft tolerance and excellent myeloma reponses.[20] One case report suggested empiric use of rituximab in preventing or delaying LCDD recurrence in renal allograft.[12]

Bortezomib, a proteasome inhibitor, is primarily used as an antineoplastic agent. It is US Food and Drug Administration approved for the treatment of MM and mantle cell lymphoma and has been used off label in kidney transplant patients with antibody-mediated rejection. Bortezomib leads to apoptosis of malignant cells by proteasome inhibition and disruption of intracellular protein production. Common side effects include skin rash, bone marrow suppression, hypotension, gastrointestinal upset, and peripheral neuropathy. In preclinical studies, bortezomib has been shown to benefit renal function in LCDD.[21] LCDD results from excessive production of a monoclonal light chain that overwhelms the absorptive mechanisms in the proximal tubules with subsequent spillage in the urine. These toxic monoclonal light chains interact with mesangial cell receptors to initiate a cascade that activates nuclear factor kappa β. Nuclear factor kappa β augments cytokine production and attracts inflammatory cells. Nuclear factor kappa β also induces platelet-derived growth factor-β and tumor growth factor-β (TGF-β), leading to cellular proliferation and collagen production and causing glomerulosclerosis. Bortezomib has been suggested to inhibit the nuclear factor kappa β pathway,[22] thereby decreasing TGF-β levels, downregulating collagen production,[23] and slowing the progression of glomerulosclerosis, with subsequent improvement in renal function.

Bortezomib is usually administered over a 3-week cycle, and patients with MM receive 6-8 cycles followed by maintenance therapy on a weekly or biweekly basis.[24,25] Bortezomib is seldom used alone and is usually reserved for patients who are refractory to first-line treatment. In a systematic MEDLINE database review of patients with MM and acute kidney injury (AKI) from 1978 to December 1, 2010, 18 studies (9 case series and 9 case-control studies) were identified in which bortezomib was a part of the treatment regimen. The only factors predictive of reversal of AKI were a bortezomib-based regimen and creatinine clearance >30 mL/min. The authors concluded that bortezomib was well tolerated in patients with renal failure, and the efficacy of bortezomib was maintained in patients on dialysis. They also found that a standard dose of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) associated with dexamethasone yielded good response, usually obtained in a short period of time.[26]

Our patient was unusual in that she had clinical response after only 1 cycle of bortezomib. Her renal function improved and she was able to discontinue dialysis. At 1-year follow-up, she had stable renal function and no evidence of myeloma based on peripheral studies. She will, however, need a follow-up bone marrow biopsy to restage her disease. Her treatment was limited because of severe neurological side effects. Decreasing the dose of bortezomib and reducing the number of treatment cycles may be a way to avoid these unfavorable side effects.

Sustained remission must be obtained in patients with LCDD before pursuing kidney transplantation. Patients with detectable light chains in the serum or urine experience worse outcomes after kidney transplantation compared with patients without detectable light chains.[17] Kidney transplantation should be reserved for patients in whom the light chain production is controlled and long-lasting remission is documented. If living-donor kidney transplantation is considered, both the donor and recipient must be thoroughly informed about the possibility of recurrence and potentially reduced lifespan of the allograft. Regardless, recurrence is common, and bortezomib may provide an alternative to currently available

treatment options in patients with LCDD recurrence after transplantation.

CONCLUSION

In contrast to traditional regimens for treatment of LCDD, a short course of bortezomib may be equally efficacious and may limit side effects. Further investigations are warranted.

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