Can We Cure Light Chain Deposition Disease of the Kidneys?—A Review and Case Report of a Patient Treated With a Triple Transplant Approach

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Clinical Practice Points

- Renal involvement is ubiquitous in light chain deposition disease (LCDD) and often progresses to irreversible end-stage renal disease (ESRD).
- Currently, no guidelines outlining the treatment of patients with ESRD requiring hemodialysis secondary to LCDD have been accepted.
- A dual approach combining autologous stem cell transplantation (SCT) with renal transplantation has shown promising results in this population of patients.
- We performed a triple approach, combining autologous SCT, renal transplantation, and nonmyeloablative allogeneic SCT in a young woman with κ-LCDD; she has remained in complete remission for > 9 years and has not required any immunosuppressive therapy.
- If complete hematologic remission is sustained in patients with LCDD with ESRD, renal transplant must be considered.
- The use of allogeneic SCT in this specific population of patients should be explored as a potentially curative option for those who have achieved remission in response to previous treatment.
- This triple approach treatment strategy could have a "curative role" in the treatment of patients with LCDD with ESRD requiring hemodialysis.

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Introduction

Monoclonal immunoglobulin deposition diseases (MIDDs) are characterized by the abnormal deposition of immunoglobulins (Igs) in various organ systems. MIDDs have been classified into 3 subtypes according to the composition of the deposits: light chain deposition disease (LCDD), the most common subtype (accounting for ≤ 80% of cases), heavy chain deposition disease, and light and heavy chain deposition disease.[1,2]

Randall et al[3] first described LCDD in 1976. It is a rare, clonal plasma cell dyscrasia categorized as an MIDD in the World Health Organization Classification of Tumors of the Hematopoietic and Lymphoid Tissues.[4] Light chains (LCs) are small protein molecules formed by plasma cells and normally excreted by the kidneys.[5] LCDD is characterized by abnormal deposition of either κ-LCs or, rarely, λ-LCs.[6] The monoclonal LCs in LCDD are overwhelmingly κ (≤ 92% of cases), and most belong to the VkIV subgroup.[1,7-9] In contrast, the λ-LCs type is more common in amyloid LC (AL) amyloidosis.[9,10] Unlike with AL amyloidosis, in which LCs are laid down in characteristic amyloid fibrils, in LCDD, these proteins are laid down in nonamyloid granules, leading to organ damage.[11] Also unlike with AL amyloidosis, the characteristic

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feature of LCDD is nonfibrillar protein deposits that do not stain with Congo red and silver stain but do stain with periodic acid-Schiff.[12,13]

The clinical presentation and symptoms of LCDD depend on the location of the deposition of LCs. Because the kidneys are the most commonly involved organs, patients typically present with hypertension, edema, and nephrotic syndrome, with ≤ 70% of the patients rapidly progressing to end-stage renal disease (ESRD) if untreated.[14] Patient age and the degree of kidney injury at presentation are well-known prognostic indicators affecting treatment-related mortality, toxicity, and the rates and duration of remission and disease progression.[11] In addition, factors such as the presence of a hematologic disorder, especially multiple myeloma (MM), and extrarenal LCDD are predictors of overall survival.[11,14]

The abnormal LCs characteristic of LCDD interact with the mesangial cells of the kidney to induce a cascade of cellular pathways, including activation of NF-κB, which lead to the production of pro-inflammatory cytokines, the recruitment of inflammatory cells, and resultant kidney damage. The most common presentation is that of nephrotic range proteinuria and rapidly declining renal function, although other organ involvement, such as that of the heart, liver, and nervous system, has also been reported.[15-17]

LCDD remains a rare clinicopathologic entity, and as a result, its true rate of occurrence is not yet known.[1] It affects males ≤ 2.5 times more than females and is generally found in association with other plasma cell disorders such as monoclonal gammopathy of undetermined significance in 17% of patients and MM in ≤ 58% of patients.[4,15,18] LCDD typically occurs during the fifth and sixth decades of life, with a median age at diagnosis of approximately 58 years, a younger median age than that for other plasma cell dyscrasias, such as MM and AL amyloidosis.[8,19]

Treatment of MIDD with high-dose chemotherapy and autologous stem cell transplantation (auto-SCT) has been reported to improve patients' renal survival and function.[20] Patients with LCDD and ESRD treated with a combination of autologous transplantation and renal transplantation have also shown promising results.[9] In the present report, we describe the case of a patient with nephrotic syndrome due to underlying biopsy-proven LCDD. She eventually underwent autologous hematopoietic SCT (auto-HSCT) followed by renal transplantation and, subsequently, allogeneic hematopoietic SCT (allo-HSCT), both from a matched sibling donor.

Case Report

We report the case of a 43-year-old caucasian woman diagnosed with LC deposition of the kidney resulting in ESRD. The patient presented with nephrotic syndrome in June 2004. She was referred to a nephrologist, and the findings from the kidney biopsy and pathologic examination were consistent with a diagnosis of κ-LCDD. The abnormal glomeruli were characterized by an expanded mesangium involved by nodular glomerulosclerosis. The interstitium showed moderate fibrosis, and the tubules demonstrated tubular atrophy, along with uniform tubular basement membrane thickening. The Congo red stain was negative; however, immunofluorescence revealed linear deposits of κ-LCs within the tubular basement membranes. The patient underwent bone marrow aspirate and biopsy, and pathologic examination showed an elevation (8%) of plasma cells, with no evidence of amyloid deposition. Shortly thereafter, she started induction therapy with thalidomide and dexamethasone. However, she soon discontinued the therapy because of fluid overload and progressive renal insufficiency. Hemodialysis (HD) was required starting in August 2004. As a part of her initial staging workup, she underwent upper and lower gastrointestinal endoscopy with gastric and rectal biopsy specimens taken. The pathologic examination findings were unremarkable.

Additional studies done at presentation included an echocardiogram, which showed mild left ventricular hypertrophy with normal left ventricular function; and pulmonary function testing, which showed a normal vital capacity, a forced expiratory volume in 1 second of 83%, a forced expiratory volume in 1 second/forced vital capacity ratio of 72%, a low forced expiratory flow at 25% to 75%, and a low diffusion capacity (diffusing capacity of the lungs for carbon monoxide of 103%). A bone scan in July 2004 showed no osseous destructive lesions.

In September 2004, the patient underwent stem cell priming with granulocyte colony-stimulating factor followed by stem cell harvest. One month later, she underwent high-dose chemotherapy with melphalan (total dose unknown) and autologous stem cell rescue. She continued to undergo dialysis throughout the procedure but experienced no major toxicities. The restaging workup performed in November 2004 included bone marrow aspiration and biopsy. The pathologic examination showed normocellular marrow with no evidence of atypical plasma cell infiltration and normal cytogenetic findings. The 24-hour urine serum protein electrophoresis (SPEP)/immunofixation electrophoresis (IFE) did now show evidence of residual free LCs, confirming that she had achieved a hematologic complete response (CR). In February 2005, the patient was evaluated by the renal transplantation team to determine her eligibility for living-related renal transplantation.

In June 2006, the patient underwent successful living-related renal transplantation from her sister, without complications. The restaging laboratory tests after renal transplantation confirmed that she had remained in hematologic CR (urine protein electrophoresis [UPEP]/IFE negative, SPEP/IFE negative, normalized free LC ratio, β_2-microglobulin of 2.3 [normal], and brain natriuretic protein within normal limits). She received prednisone, mycophenolate (CellCept), and tacrolimus (FK506) as her immunomodulatory regimen after renal transplantation.

In December 2006, she underwent a nonmyeloablative-matched related allogeneic transplantation from the sister who had donated her kidney as a full-matched stem cell donor (human leukocyte antigen typing). Her conditioning regimen consisted of fludarabine 30 mg/m^2 daily for 4 days (57 mg/d) on days −5, −4, −3, and −2, cyclophosphamide 950 mg/d intravenously for 4 days on day-−5, −4, −3, and −2, alemtuzumab 20 mg/d intravenously for 5 days, followed by peripheral blood stem cell reinfusion on days 0 and +1. The total dose of CD34$^+$ cells was 7.56 × 10^6 CD34$^+$/kg. Her post-transplant course was complicated by cytomegalovirus reactivation, requiring treatment with ganciclovir.

At 3 months after transplantation, in March 2007, the peripheral polymerase chain reaction-restriction fragment length polymorphism-based analysis finding was still < 2% donor. We monitored this twice and also performed a serum free LC assay test that confirmed disease remission (free light chain [FLC]-κ, 0.40; FLC-κ/λ ratio, 0.73). We, therefore, pursued a second