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Light chain deposition disease: novel biological insights and treatment advances

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SUMMARY

Light chain deposition disease (LCDD) is a monoclonal gammopathy characterized by nonamyloid deposition of immunoglobulin light chains in various organs. Most cases present with renal dysfunction, a ubiquitous feature of this disease, and in some instances, it may progress to end-stage renal disease. Unfortunately, until now, no standard treatment has been established. The use of alkylating agents and steroids has been extensively reported. However, conventional chemotherapy response is generally limited with minor effects on kidney function. The use of novel agents such as bortezomib has shown a more rapid response with a dramatically important reduction of light chains in serum and/or urine in small series of cases. Furthermore, autologous stem cell transplantation has been reported as a feasible strategy in LCDD, able to prolong the dialysis-free survival. Nonetheless, toxicity from these therapies should be considered carefully because most of patients might present with kidney dysfunction that could limit the use of some agents.

INTRODUCTION

Light chain deposition disease (LCDD) is categorized in the family of 'monoclonal immunoglobulin deposition diseases' (MIDD) in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [1]. This disorder was originally described by Randall *et al.* [2] in 1976 in two patients with end-stage renal disease (ESRD) with granular deposition of free light chains that did not stain with congo red on kidney pathologic evaluation. LCDD is a rare clinicopathologic entity characterized by tissue deposition of nonamyloid immunoglobulin light chains [3]. A single clone of plasma cells is responsible for the overproduction of either kappa or rarely lambda light chains [4]. Even in the absence of detectable serum or urine monoclonal immunoglobulin, a monoclonal population of bone marrow plasma cells can be demonstrated via immunofluorescence, and an altered serum-free light chain ratio is usually seen [5]. The median age at diagnosis for LCDD is 58 years, representing a younger population when compared to MM [6]. LCDD affects men 2.5 times more often than women [7] and is usually

associated with monoclonal gammopathies of undetermined significance in 17% of patients and MM in 58% [1].

CLINICAL FEATURES

Renal involvement

Light chain deposition disease can occur virtually in any organ [8]. Renal involvement is consistently present and is characterized by proteinuria and microscopic hematuria. In most patients with LCDD, renal function declines rapidly as a rapidly progressive glomerulonephritis [6] or as an acute tubulointerstitial nephritis [1], which is because of progressive accumulation of light chains from plasma filtration and includes proteinuria, nephrotic syndrome, and/or renal failure. Interestingly, albuminuria levels do not correlate with the existence of nodular glomerulosclerosis and may occur in the absence of significant glomerular lesions as detected by light microscopy [9]. Renal failure occurs with comparable frequency regardless of the level of light chain excretion. In addition, patients with LCDD might present at diagnosis with hypertension (Table 1).

Table 1. Clinical features in light chain deposition disease

Characteristic	
Age [6]	Median 58 years
Gender/Ratio [1]	Male/Female, 2.5
Hypertension [6]	53%
Hematuria [6]	45%
Median creatinine at diagnosis umol/L [40]	232
Median level of proteinuria at diagnosis (g/day) [40]	3.74
Median kappa/lambda ratio (kappa restricted cases only) [40]	36.1
Monoclonal protein (serum/urine) [30]	88%
Kappa light chain [10]	92%
Multiple myeloma [1, 53]	50–58%
Organ involvement	
Renal [7, 54]	93–100%
Liver [55]	23%
Polyneuropathy [26]	20%

RENAL PATHOLOGY

The characteristic morphologic features of renal LCDD include the following: nodular sclerosing glomerulopathy by light microscopy; diffuse linear staining of glomerular basement membranes (GBM) and tubular basement membranes (TBM) for a single light chain (LCDD) by immunofluorescence; and nonfibrillar, 'powdery' electron dense deposits in GBMs and TBMs detected by electron microscopy [10]. The mesangial nodularity within the glomerulus results from the combined increased deposition of extracellular matrix (ECM) proteins mixed with monotypic light chain deposits, most commonly kappa (κ; 92%) and the majority VK_{IV} subgroup [10]. In LCDD, all kidney tissue specimens should be stained for κ and λ light chains. The majority of cases exhibit monotypic light chain (mostly κ) fixation along tubular basement membranes. This criterion is required to be fulfilled for the diagnosis of LCDD [11–13]. The tubular deposits stain strongly and predominate along the loops of Henle and the distal tubules, but they also often are detected along the proximal tubules. Light chain Fanconi syndrome attributed to proximal tubular involvement should be differentiated. This entity typically manifests with type II renal tubular acidosis, hypophosphatemia, glycosuria, and hypouricemia. Heart, liver, and other organs are less frequently involved [14].

Extrarenal involvement

Symptomatic extrarenal deposition is rare. It is uncertain whether or not localized LCDD really exists or represents an initial expression of a silent systemic LCDD [15].

Liver involvement

In LCDD, the liver is the most frequent extra-renal site (23%) [7, 16], but involvement is not generally isolated to this organ. The degree of liver dysfunction does not seem to correlate with the amount of light chain deposition in the liver [16]. Affected patients may develop hepatic insufficiency and portal hypertension, and some die with hepatic failure [7].

Heart involvement

Cardiac involvement could be associated with heart enlargement, restrictive cardiomyopathy, and severe

congestive heart failure [17–19]. Increase in brain natriuretic peptide and troponin-I has also been seen in patients with LCDD (Jimenez-Zepeda *et al.*, data not published). However, the role of these biomarkers in LCDD prognostication has not been reported yet. Echocardiography and catheterization may reveal diastolic dysfunction and reduction in myocardial compliance similar to that found in cardiac amyloid [20]. It is thought that cardiac involvement translates into a worse outcome. However, there is lack of data to support this association.

Lung involvement

Light chain deposition disease infrequently affects the lungs and usually causes damage to the parenchyma, while bronchial involvement appears to be very rare. However, the involvement of the large airways has been recently reported [21]. Nodular and diffuse pulmonary interstitial diseases have been described, but, to date, only seven cases of pulmonary nodular-type LCDD are reported in the literature. [22–24].

Neurological involvement

Systemic protein deposition may affect the nerves similar to that seen in amyloidosis, clinically manifested by polyneuropathy (occurring in 20% of the reported cases) [25]. Deposits may occur along the nerve fibers and in the choroids plexus [26]. Isolated LCDD in the brain has also been described [27]. It is thought that generally the blood–brain barrier protects the central nervous system (CNS) from the circulating, polymerized, misfolded proteins, preventing any type of systemic amyloidosis or systemic nonamyloid monoclonal deposition disease causing any harm to the CNS. However, cases of intracerebral amyloidomas and LCDD have been reported in the literature [28].

Other sites

Deposits can also occur in the lymph nodes, bone marrow, spleen, pancreas, thyroid glands, gastrointestinal tract, adrenal glands, abdominal vessels, lungs, and skin [8].

Association with other B-cell malignancies

Light chain deposition disease could be associated with multiple myeloma in 58% of cases [1]. LCDD, similar to that seen in AL amyloidosis, often is the primary discovered disease that leads to the investigations for an underlying plasma cell proliferative disorder at an early stage. LCDD could be present at diagnosis of a new plasma cell disorder or could represent an extramedullary manifestation of MM while relapsing after chemotherapy [20]. LCDD occasionally may complicate the course of lymphoplasmacytic lymphoma, chronic lymphocytic leukemia, and marginal-zone lymphoma [29]. A monoclonal plasma cell population in bone marrow is rarely identified by immunofluorescence in clinical laboratories. The preferred method is *in situ* hybridization or flow cytometric analysis.

Diagnostic approach

Patients suspicious to suffer from LCDD should be assessed by using the screening panel for patients with plasma cell proliferative disorders (PCPD; Table 2) [30]. The recent introduction of quantitative serum assays for immunoglobulin free light chain (FLC), however, has increased the sensitivity of laboratory testing strategies for identifying monoclonal gammopathies [31]; this increased diagnostic sensitivity is readily apparent in the monoclonal light chain diseases [32]. Because of the increased sensitivity for free light chain diseases [33], the most recent diagnostic screening recommendations are that serum IFE plus FLC is a sufficient screening panel for PCPD other than AL and LCDD. It is recommended, however, that screening for AL and LCDD should also include urine IFE [30]. When you combine serum PEL, FLC and IFE, and urine PEL/IFE, the sensitivity for LCDD goes up to 83.3% and decreases to 77.8% if you omit the use of urine for PEL and IFE. Excluding FLC decreases the sensitivity for LCDD detection to 77.8%. Patients with extensive proteinuria, rapidly progressive renal failure, and organ dysfunction such as congestive heart failure or liver should be suspected to have LCDD. Because sensitive techniques as mentioned earlier can miss a monoclonal component detection in approximately 10–15%, kidney biopsy is important to guide an adequate and prompt diagnosis of LCDD [8, 9, 34]. The confirmation of LCDD diagnosis is made by the immunohistologic analysis of tissue from an affected organ, which is not congophilic in nature. Light chain restriction analysis on the tissue will confirm whether the light or heavy chain is monoclonal. When a patient is diagnosed with

Table 2. Assessment of patients suspicious of light chain deposition disease (LCDD)

Evaluation	
Past Medical History	History of PCPD or autoimmune disorders
Physical Examination	Blood pressure, hepatomegaly, splenomegaly, lymph nodes
Laboratory assessment	CBC, electrolytes, creatinine, calcium, magnesium, ALP, AST, ALT, bilirubin, albumin, LD, creatinine clearance, and proteinuria
Protein assessment	SPEP + IFE + FLC + UPEP + Urine IFE (sensitivity 83%, LCDD)
Additional organ assessment	
Kidney	Renal biopsy (congo red staining, immunohistochemistry, immunofluorescence, electron microscopy)
Liver	Liver ultrasound, biopsy if indicated
Heart	Echocardiogram, BNP, troponin-I, biopsy if indicated
Nerve	Electrophysiological studies, biopsy if indicated
Lung	CT scan if highly suspicious of lung involvement
Plasma cell-associated disorder	Bone marrow aspirate and biopsy Flow cytometry, immunohistochemistry, and FISH cytogenetics if myeloma is confirmed Congo red staining on bone marrow Skeletal survey

PCPD, plasma cell proliferative disorder; SPEP, serum electrophoresis; FLC, free light chains; IFE, immunofixation; UPEP, urine protein electrophoresis; BNP, brain natriuretic peptide.

LCDD, workup should include echocardiogram and abdominal ultrasound to assess liver, spleen, and lymph nodes. Bone marrow aspirate and biopsy should be performed to rule out the presence of MM and/or light amyloidosis. We highly recommend performing tests for troponin-I or T and brain natriuretic peptide (BNP) because LCDD may mimic biologically AL amyloidosis and these markers have been reported as predictors of survival in that disease (Figure 1). Nerve studies and CT, MRI, or PET scans should be considered in an individual basis [26, 35]. After a biopsy confirms the diagnosis of LCDD, there is no need for additional biopsies unless there is a clinical implication (i.e. cardiac biopsy to rule out other possibilities, or assessment pretransplant).

Treatment

As the clinical presentation in LCDD is known to depend on the number and nature of organs affected, deposition of different light chains does not seem to affect their clinical course [36]. The median duration of survival is approximately 4 years. After a median follow-up of 27 months, the largest series to date reported that 57% of cases reached uremia and 59% died [6]. Prognostic factors for LCDD include age, presence of plasma cell myeloma, and extrarenal light chain deposition [1, 10]. Dialysis patients seemed to achieve the same outcome in comparison with those who did not reach uremia. The adequate treatment of LCDD has not been established and is indicated for those patients with systemic disease, severe and symptomatic renal dysfunction, and active concomitant symptomatic MM. Unlike multiple myeloma, the plasma cell burden is usually low (5% plasma cells or less). The cells do not have a high proliferative rate and frequently lack the genetic abnormalities that are associated with an adverse prognosis in multiple myeloma. A single course of high-dose chemotherapy can, therefore, result in long-term suppression of the plasma cell clone, producing durable responses for such patients (MGUS-like phenotype). However, in those with MM associated with LCDD, the disease should be treated according to the myeloma guidelines because the prognosis is generally poor [37]. There is lack of evidence to suggest maintenance therapy for patients with LCDD. However, the experience in MM indicates that chronic treatment perhaps should be required to obtain a better control in this disease. An anecdotal report suggests that the use of thalidomide maintenance could be feasible to improve and stabilize LCDD response [38]. Guidelines in this regard are needed, and currently, suppression of light chain production should be the goal of therapy to avoid further deposition in organs not yet affected. In addition, medical management for the organ dysfunction should be provided. For instances, some patients might benefit from the use of ACE inhibitors to decrease proteinuria, and renal failure patients may require some form of dialysis as a function replacement strategy.

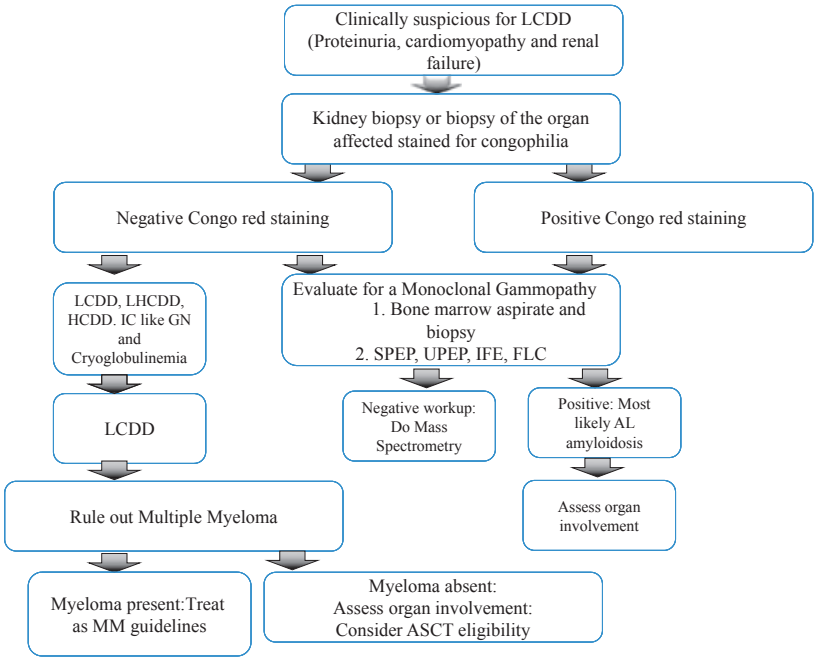

Figure 1. Diagnostic approach for LCDD. SPEP, serum electrophoresis; FLC, free light chains; IFE, immunofixation; UPEP, urine protein electrophoresis; GN, glomerulonephritis; IC, immune complexes; MM, multiple myeloma; LCDD, light chain deposition disease.

Table 3. Treatment options for light chain deposition disease

Therapy	Hematological response (HR)	Dialysis-free Survival (DFS)
Alkylating agents	NA	37% at 5 years [6]
Thalidomide	Single case report, patient achieved complete HR [47]	Dialysis free at 30 months, single case [47]
Lenalidomide	NA, single case report [48]	NA, single case report [48]
Bortezomib	Induction therapy (3 cases), 100% HR, 33% organ response at 6 months post-ASCT [45]	100% at 1 year [45]
	Induction therapy, 100% HR (2 cases), 100% organ response at 6 months post-ASCT [40]	100% at 2 years [40]
	Bortezomib, doxil, and dexamethasone (1 case) for 6 cycles, followed by thalidomide maintenance (PR after 3 cycles) [38]	Dialysis free at 32 months [38]
	Bortezomib and dexamethasone (4 cases), 100% HR, 2 CR and 2 PR, 3 responses at a median of 3 weeks of treatment, 3 cases followed by ASCT, PFS at 15, 16, and 12 months [46]	100% at 16 months [46]
Autologous stem cell transplant	100% HR, 3 cases with MM, 1 patient on hemodialysis, induction with dexamethasone [5], 100% organ response after 6 months [39]	DFS 83% at 32 months [39]
	100% HR, 5 cases, 3 CR, 1 PR and 1 SD, PFS at 20 months [40]	DFS 100% at 20 months [40]
	100% HR, 1CR, 8 cases, 2 relapses, 7/8 renal responses [41]	DFS 100% at 24 months [41]

NA, Not available.

AUTOLOGOUS STEM CELL TRANSPLANTATION

The use of high-dose chemotherapy for LCDD followed by autologous stem cell transplantation (ASCT) has been reported (Table 3) [39, 40]. Stem cell transplantation is believed to be a good strategy to produce durable responses in a disease such as LCDD where the plasma cell burden is usually low and the cells do not have a high proliferative rate and most of times lack of adverse genetic abnormalities as in MM. Generally, stem cell mobilization is performed by using G-CSF alone, and melphalan is adjusted to 140 mg/m^2 in an attempt to ameliorate the morbidity in cases with renal insufficiency. Recently, the report of eight cases of MIDD treated with high-dose melphalan was published (HDM) [41]. Of the five evaluable patients for a hematological response, all responded with one complete response. A renal response was seen in 7/8 patients. Furthermore, a long-term analysis on six patients with LCDD transplanted at Mayo Clinic showed that ASCT might be an effective therapy for renal dysfunction associated with LCDD [39]. Median reduction of proteinuria was 92%, and median improvement of estimated glomerular filtration rate (eGFR) was 95%. The authors of this report suggested that in cases where kidney dysfunction persists after ASCT, a hematological response may permit successful kidney transplantation with improved graft viability and decreased risk recurrence. Unfortunately, until now there is no clear data to support this approach.

Bortezomib

In LCDD, toxic monoclonal light chains interact with receptors in mesangial cells initiating a cascade of activation of pathways that include the NFκB pathway. NFκB activation results in stimulation of cytokine production causing attraction of inflammatory cells. This results in cell proliferation and activation of genes responsible for collagen and tenascin production, resulting in dramatic changes in mesangial matrix, leading to the pathological picture of glomerulosclerosis [10]. Bortezomib inhibits the NFκB pathway, decreases TGF-B1 levels, and may downregulate collagen and TIMP-1 production [42]. Thus, bortezomib may interrupt the cascade that leads to rapid renal deterioration through these pathways by inhibiting progression of glomerulosclerosis and may improve glomerular function, thus reducing proteinuria [43, 44].

Bortezomib-based induction chemotherapy

Recently, the use of bortezomib in small series of patients with LCDD has been reported. First, a series of three patients with LCDD treated with induction bortezomib-based regimen was reported [45]. The treatment led to a rapid hematological response with a median of two cycles based on a decrease in FLC levels. Another group reported on four cases with LCDD treated with bortezomib and dexamethasone as induction therapy before ASCT [46]. Responses were seen rapidly, and 2/4 patients achieved complete hematological response (CR). In addition, our group reported the use bortezomib and dexamethasone induction in two cases before ASCT. Both cases achieved PR as the best response after three cycles of therapy and organ response at 6 months post-transplant [40]. These data together suggest that induction chemotherapy may help ameliorating the renal dysfunction seen in LCDD and perhaps would lead to a more feasible approach with HDM and ASCT with a better outcome. The role of induction chemotherapy in LCDD should be investigated in a prospective manner.

Immunomodulatory drugs

Thalidomide, an immunomodulatory drug, has multiple mechanisms of action as an anti-myeloma agent. Numerous studies have shown the efficacy of thalidomide in the treatment of AL amyloidosis and myeloma. However, the use of thalidomide in LCDD has not been extensively evaluated. A recent report suggests that thalidomide in combination with dexamethasone is a feasible drug able to provide a durable hematological response for a single case of LCDD, achieving a 31-month remission, which also led to improvement of the renal insufficiency [47]. In addition, a case of LCDD associated with MM with severe liver involvement treated with melphalan, prednisone, and lenalidomide was reported. Unfortunately, the patient developed intrahepatic ischemic cholangitis, and thus, lenalidomide was discontinued. The role of lenalidomide in LCDD remains to be elucidated [48].

RENAL TRANSPLANTATION

A small number of kidney transplantations have been performed on LCDD in whom end-stage renal (ESRD) disease developed [49]. Although long-term benefits are occasionally seen, renal allograft survival is reduced significantly in patients with LCDD. Despite treatment pretransplantation, LCDD patients with detectable LCs in the serum or urine tend to experience worse clinical courses after grafting with early devastating recurrences [50]. Thus, kidney transplantation should be reserved for patients with relatively benign courses, whose light chain production can be controlled by directed therapy removing the nephrotoxic light chains from the circulation with sustained remission. If kidney transplantation is considered, both the donor and recipient must be thoroughly informed about the potentially reduced life span of the allograft. Nonetheless, unforeseen recurrence may develop, even shortly after transplantation, and may be confused with an acute rejection episode. A recent report suggests that bortezomib may successfully reverse early recurrence of LCDD in a renal allograft [51]. The role of bortezomib induction followed by ASCT and the possibility of renal allografting if complete remission is achieved remains to be explored. Furthermore, the use of rituximab for delaying early LCDD recurrence in patients in whom treatment for underlying bone marrow disorder failed or is contraindicated has been suggested [52]. However, it seems that maintenance therapy should be necessary to consolidate this response.

Toxicity considerations

Overall high-dose chemotherapy and ASCT led to the expected toxicities of bacteremia, diarrhea, and mucositis. While treating patients with LCDD, age and comorbidities should be carefully considered. Patients with LCDD are younger than those with MM allowing the possibility of ASCT as a therapeutic option. However, the coexistence with MM and the number of organs affected, including the presence of cardiac involvement, might predict a worst outcome. Multi-systemic organ failure after transplantation has been reported in patients with extrarenal manifestations of LCDD (notably, cardiac involvement). This finding might signify high risk for complications and death, and thus, patients should be carefully assessed before the decision of undergoing ASCT is made [39]. Moreover, ASCT should be performed in centers with expertise in this type of conditions to decrease morbidity and mortality.

CONCLUSION

Light chain deposition disease is a systemic disorder characterized by deposition of monoclonal light chains in various organs. It should be distinguished from Fanconi syndrome, myeloma cast nephropathy, cryoglobulinemia, and amyloidosis, all of which are also associated with monoclonal proteins. Therapy to achieve complete suppression of light chain production is indicated. Disease control appears to be most easily achieved using bortezomib chemotherapy, ASCT or both. However, despite all of the published studies, the experience of ASCT, lenalidomide, and bortezomib in this disease remains small, and prospective studies in this regard are needed.

AUTHORSHIP

Victor H Jimenez-Zepeda designed and wrote the manuscript.

DISCLOSURES

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