Light chain deposition disease. Experience in our environment

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SUMMARY

The Light chain deposition disease (LCDD) is a strange entity characterised by the deposition of only one type of light chain in the renal tubular basement membranes. It can be associated to a plasma cell dyscrasia, however, it can occur in the absence of any detectable hematological disorder and it is called idiopathic LCDD. The clinical manifestation is renal insufficiency and nephrotic proteinuria, it does not have a clearly fixed treatment and has a severe prognosis. The aim of this work is to analyse the characteristics of the LCDD cases diagnosed within our environment.

Six cases were identified, all of them between 1999 and 2005, from a total amount of 640 renal biopsies performed during this period, 4 women and 2 men, average age of 57. Multiple myeloma in 3 patients was detected (50%). The acute renal failure or rapidly progressive renal insufficiency was the most frequent clinical presentation (66%) together with nephrotic proteinuria (66%). All the biopsies showed tubular basement membranes thickening and kappa chains with a linear distribution within the same. The most frequent glomerular pathological finding was the nodular sclerosing glomerulopathy (83%). In one of the cases the affectation was exclusively tubular interstitial with tubular casts. 3 patients were treated, 2 with multiple myeloma. 5 patients needed dialysis: 3 with idiopathic LCDD within an average time of 7 days from the diagnosis to its reception, and 2 with myeloma, who started needing dialysis in an average of 46 days. 4 patients died, 2 of them with myeloma. The monitoring time until the death was 13 weeks for the patients with myeloma and 110 weeks for the rest.

Conclusion: *The LCDD seems to be more frequent than what has been published and it is associated to the myeloma in half of the cases. It appears together with severe renal insufficiency and the patient's and renal prognosis is poor.*

Key words: *Light chain nefropathy. Nodular sclerosing glomerulopathy. Plasma cell dyscrasia. Monoclonal gammopathies.*

RESUMEN

La enfermedad por depósito de cadenas ligeras (EDCL) es una entidad rara, caracterizada por el depósito de un solo tipo de cadena ligera en la membrana basal del riñón. Puede asociarse a una discrasia de células plasmáticas, aunque en ocasiones no se detecta patología hematológica y se denomina idiopática. Suele manifestarse como una insuficiencia renal severa con proteinuria nefrótica, no tiene tratamiento claramente establecido y el pronóstico es malo. El objetivo de este trabajo es analizar las características de los casos de EDCL diagnosticados en nuestro medio.

Se identifican 6 casos, todos entre 1999 y 2005 de un total de 640 biopsias realizadas en ese periodo, 4 mujeres y 2 varones, media de 57 años. Se detectó un mieloma en 3 pacientes (50%). La insuficiencia renal aguda o de rápida evolución fue la presentación clínica más frecuente (66%) junto con proteinuria nefrótica (66%). Todas las biopsias mostraban engrosamiento de la membrana basal tubular y depósito lineal de cadenas kappa en la misma. La lesión glomerular más frecuente fue la glomeruloesclerosis nodular (83%). En un caso la afectación fue exclusivamente túbulo intersticial con cilindros tubulares asociados. Se trataron 3 pacientes, 2 con mieloma. Requirieron diálisis 5 pacientes: 3 con EDCL idiopática con un tiempo medio desde el diagnóstico hasta recibir la misma de 7 días, y 2 con mieloma que tardaron una media de 46 días en requerir diálisis. Fallecieron 4 pacientes, 2 con mieloma. El tiempo de seguimiento hasta el exitus fue de 13 semanas para los pacientes con mieloma y de 110 semanas para el resto.

Conclusión: **la EDCL parece más frecuente de lo publicado y se asocia a mieloma en la mitad de los casos. Se presenta con daño renal severo y la evolución renal y del paciente es mala.**

Palabras clave: Nefropatía por cadenas ligeras. Glomeruloesclerosis nodular. Discrasia de células plasmáticas. Gammapatía monoclonal.

INTRODUCTION

B-cell proliferative diseases are usually associated to production and secretion into blood of a monoclonal immunoglobulin, or a fragment of it, that may be deposited in the organs in an organized form as crystals, fibrils or microtubules, or in a non-organized form (granular). This immunoglobulin will mainly be deposited in the kidney, not only because this is a highly vascularized organ, but also because the renal tubule has a predominant role in immunoglobulin metabolism.[1] Diagnosis of renal involvement due to immunoglobulin deposition is being expanded with development and routine implementation of different laboratory procedures (staining with antibodies specific to kappa and lambda light chains, electron microscopy study, development of procedures with an increa-

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sing sensitivity for detecting the monoclonal component in blood or urine).[2] Light chain deposition disease (LCDD) is characterized by generalized deposition of a single type of light chain along the renal basement membrane. LCDD is usually reported to occur during plasma cell dyscrasia or another lymphoproliferative disorder, but may also occur in the absence of any hematological disorder, in which case it is called idiopathic LCDD. Severe renal insufficiency occurs in most patients despite treatment.[3,4] The most typical renal lesion is nodular glomerulosclerosis, in which mesangial nodules and deposition of a single chain type occur along the glomerular basement membrane. However, diagnosis will be based on light chain deposition along the tubular basement membrane. The aim of this study was to review our experience with this uncommon disease.

MATERIALS AND METHODS

Cases of LCDD diagnosed at our hospital among all adult biopsies performed in the 1978-2005 period were analyzed. Clinical and pathological data and patient course were studied based on clinical records and on the information provided by physicians with whom the patient was in direct contact at the time of study closure. All renal biopsies taken during the abovementioned period were read by the same pathologist. All samples diagnosed as LCDD had been processed for study with light microscopy (LM) and immunofluorescence (IF). Samples from five patients were also analyzed using electron microscopy (EM). Diagnosis of LCDD was made by an IF study, in which sera against kappa and lambda light chains are used. This procedure has been routinely performed at our hospital since 2002. The presence of nodular glomerulosclerosis, chain deposit distribution, thickening of basement membranes, extent of tubulointerstitial involvement, and the presence of associated renal involvement from myeloma kidney are analyzed. Acute renal failure (ARF) or rapidly progressive renal insufficiency (RPRI) was defined as the presence of renal failure at the time of renal biopsy with a normal prior renal function or a doubling of basal creatinine in a short time period (less than 30 days). Patients who had known renal damage for a period longer than 30 days with renal function data similar to those found at diagnosis and patients with ultrasonographically small and poorly differentiated kidneys were diagnosed chronic renal failure (CRF). Screening for plasma cell dyscrasia was based on previously established criteria.[5] Bone marrow cellularity was studied in five patients, and flow cytometry was also performed in two of these patients. Blood electrophoresis was performed in all patients, and light chains were studied in the urine of five of them using nephelometry. Immunofixation in blood or urine was not available in any case. Patients with clinical data suggesting involvement of other organs were considered to have extrarenal involvement due to light chain deposition.

RESULTS

Six cases of LCDD, all of them diagnosed in the 1999-2005 period, were identified in four female and two male patients with a mean age of 57 years (range, 37-74). All patients had advanced renal failure and proteinuria at diagnosis, with mean plasma creatinine levels of 4.3 ± 1.59 mg/dL and proteinuria of 4.3 ± 1.7 g/24 h. Four patients (66%) showed acute or rapidly progressive renal damage, and two patients had chronic renal failure. Blood electrophoresis detected no monoclonal peaks in any case. Hypogammaglobulinemia was found in 5 patients (83.3%). In a patient, light chain study in urine showed a selective elevation of the kappa light chain suggesting a monoclonal peak (this patient was subsequently diagnosed of myeloma).

Bone marrow was studied in 5 patients. Of these, three patients were diagnosed of myeloma, two based on the bone marrow study and one on the lytic images seen. All bone marrow aspirates showed a proportion of plasma cells lower than 10%, and myeloma was diagnosed based on a cytometry study in the two patients in whom this was performed. LCDD was the first sign of the disease in all 3 patients with myeloma. No evidence of myeloma or other plasma cell dyscrasia was found in 3 patients.

Table I shows the characteristics of renal biopsies. They all showed thickening and kappa chain deposits in the tubular basement membrane. A nodular pattern (fig. 1) with kappa chain deposition in GBM, Bowman's capsule, and mesangium (fig. 2), was seen in 5 patients (83.3%). A patient showed tubulointerstitial involvement with lymphoplasmocytic infiltrate in interstitium and casts with peripheral cellular reaction and kappa chain deposition in casts and TBM.

Table I. Most charasteristic data from renal biopsies

	Glomerulus	Tubulo-interstitium	Vessels
BM	Nodular expansion of mesangium (6)	TBM thickening 6 (6) Tubular atrophy + interstitial fibrosis 4 (6) Lymphoplasmocytic infiltrate 1 (6) Tubular casts 1 (6)	Atherosclerosis 1 (6) Intimal hyperplasia 1 (6)
IF	k deposits in GBM 2 (6) k deposits in mesangium 3 (6)	Linear TBM stain 6 (6) for k	k deposits 3 (6)
EM	GBM deposits 5 (6) Mesangial deposits 4 (5)	TBM deposits 5 (5)	Deposits 3 (5)

LM: Light microscope. IF: Immunofluorescence. EM: Electron microscope. TBM: Tubular basement membrane. GBM: Glomerular basement membrane. In brackets, total number of biopsies analyzed.

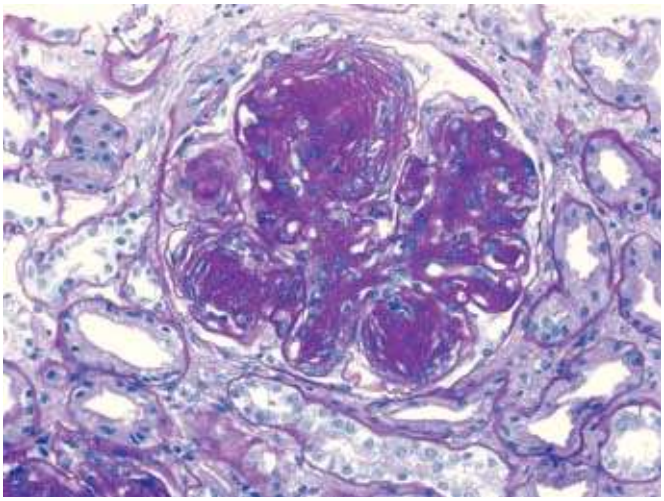

Figure 1. Glomerulus with nodular transformation and homogeneous, banded thickening of the basement membranes of glomerular capillaries and tubules. PAS stain. Micrograph, medium enlargement.

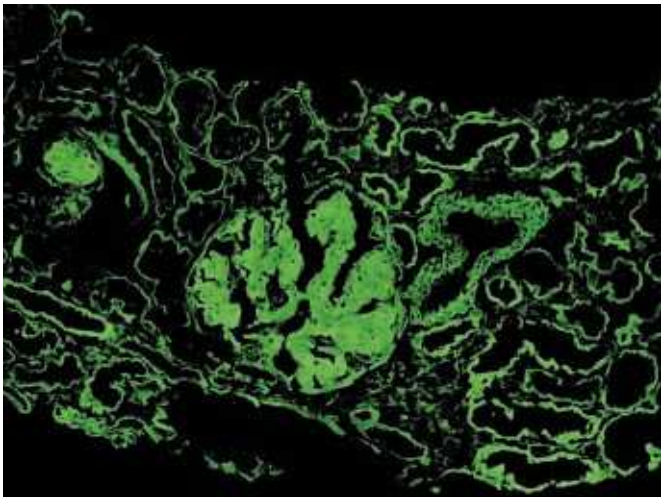

Figure 2. Diffuse and strong positive reaction with anti-kappa in tubular basement membranes, glomeruli, and arterial walls. Direct immunofluorescence. Medium enlargement.

Hemodialysis had to be started in 5 patients (4 with ARF or RPRI and one with CRF). Two of these patients had myeloma. Mean time from diagnosis to start of dialysis was 46 days (range, 0-180). In patients diagnosed of myeloma and idiopathic LCDD, times to start of dialysis were 96 days (range, 13-180) and 7 days (range, 0-13) respectively. A patient had heart failure and episodes of paroxysmal atrial fibrillation with echocardiographic (left ventricular hypertrophy) and electrocardiographic (relative microvoltage) evidence suggesting cardiac involvement from immunoglobulin deposit.

Three patients were given immunosuppressive treatment. Two patients diagnosed of myeloma received VAD cycles (vincristine, adriamycin, dexamethasone), and one patient with idiopathic LCDD was treated with corticosteroids. The third patient diagnosed of myeloma died 15 days after admission from an infectious complication and did not receive chemotherapy. The patient with idiopathic LCDD was treated for only four months because she developed catheter-induced bacteremia that required corticosteroid discontinuation. She died at two years of follow-up.

Follow-up time from diagnosis to death or study closure was highly variable (15 days-59 months), with a mean of 27 months. Mean follow-up time was 15 months in myeloma patients (15 days-40 months) and 38 months (26-54 months) in idiopathic LCDD. Of the 4 patients who died (66.6%), 2 had myeloma. Mean survival of myeloma patients was 13 weeks (one died at 15 days and the other at six months), as compared to a mean survival of 110 weeks in patients with idiopathic LCDD (one died at 26 months and the other at 29 months).

Two of the 6 patients studied, one diagnosed idiopathic LCDD and the other myeloma, were still alive at study closure. The patient diagnosed of idiopathic LCDD continues on dialysis after almost 5 years of follow-up, has not experienced involvement of other organs or a malignant hematological disease, and is in a waiting list for receiving a kidney transplant, though indication of this treatment is doubtful according to some authors.[6,7] The myeloma patient has a stable renal function after receiving chemotherapy, with no requirement of replacement therapy after 40 months of follow-up.

DISCUSSION

Necropsy studies in myeloma patients have found renal involvement by LCDD in 5% of cases. However, the frequency with which the disease is diagnosed is much lower.[8] All our cases were diagnosed from 1999 to 2005 among the total 640 renal biopsies performed during this period, representing a LCDD rate of 1%, greater than reported in other series.[8,9] In our analysis, LCDD was more frequent in females and occurred in middle-aged people, though it cannot be ruled out in young people.

Unlike the findings in other series, a monoclonal peak could not be detected in blood or urine from any patient, which may possibly be related to the sensitivity of the diagnostic procedures used. Hence, blood and urine immunofixation should be requested, either routinely or if a strong clinical suspicion exists, even if electrophoresis is normal. However, even sensitive procedures such as immunofixation are not able to detect a monoclonal peak in up to 30% of cases. Renal biopsy therefore plays an essential role in diagnosis of LCDD and its associated dysproteinemia, as evidenced by this and other studies.[10] Most of our patients had hypogammaglobulinemia and albuminuria, and these findings should therefore lead to suspect some form of immunoglobulin deposition disease, as suggested by other studies.[11,12] Clinically, LCDD started in most of our patients as an ARF/RPRI associated to nephrotic proteinuria. Since no monoclonal peak was detected in blood and urine from any of our patients, LCDD should also be suspected in the event of renal failure and proteinuria of an unknown origin. Renal biopsy is required for diagnosis.

In all our patients, the chain deposited in the kidney was of the kappa type. This is the chain primarily deposited in

LCDD according to all series, unlike in amyloidosis, where the lambda chain is deposited.[13,14] The classical pattern of nodular glomerulosclerosis was found in most of our biopsies (83%), and tubulointerstitial involvement alone, with lymphoplasmocytic infiltration, occurred in one patient. Bone marrow study is not always diagnostic, and routine staining with anti-kappa and anti-lambda sera would therefore be required to prevent the disease from being undiagnosed.

Diagnosis of myeloma may be made with a flow cytometry study,[5] but as this analysis is not performed in many hospitals, marrow cellularity continues to be a diagnostic criterion together with the monoclonal peak in blood or urine and involvement of other organs. The proportion of plasma cells in bone marrow was not higher than 10% in none of our patients, so that if this criterion is applied, myeloma diagnosis may be delayed. Thus, when plasma cell dyscrasia such as LCDD is strongly suspected, plasma cell phenotype would have to be determined to rule out a hematological tumor pathology. This happened with one of our patients, who underwent two bone marrow aspirations with a one month interval. Cellularity was similar in both samples (5%), but flow cytometry performed in the second aspirate provided a diagnosis of myeloma.

Dialysis requirements were high (83%) for the whole group, but particularly for patients with idiopathic LCDD, all of whom required dialysis and at an earlier time than the myeloma group.

Chemotherapy, which is unquestionable in myeloma patients, is controversial when no malignant disease exists. However, general practice has consisted of treatment with corticosteroids plus melphalan, regardless of the associated hematological disease, although myeloma patients more frequently receive VAD cycles, which appear to have a protective effect upon patient survival.[15-18] Recent studies showed disappearance of light chain deposits in the kidney after treatment with chemotherapy and bone marrow transplantation,[17,19] which would support intensive therapy in patients with LCDD. Two of our myeloma patients received VAD cycles, and renal function improvement was achieved in one of them.

Mortality was high in our patients. The same number of patients died in the myeloma and the idiopathic LCDD groups, but the mean follow-up time from diagnosis to death was longer in patients with idiopathic LCDD (110 *vs* 13 weeks). This, combined with the longer follow-up time in patients with idiopathic LCDD (38 *vs* 15 months), suggests that the presence of myeloma in the setting of LCDD shortens patient survival, as seen in other series (20), though there are reports that do not support these data (4,6).

To sum up, the number of patients with a diagnosis of LCDD detected in our series was higher than expected according to literature. Wider studies would be required to confirm these results. LCDD was associated to a myeloma in half of our patients, and its first manifestation was renal involvement. The predominant clinical sign was acute renal function impairment with nephrotic proteinuria that required dialysis. The structural lesion most commonly associated is nodular glomerulosclerosis. Renal and patient survival was poor.

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