

## Treatment of idiopathic light chain deposition disease: complete remission with bortezomib and dexamethasone

Tratamento da doença de depósito de cadeia leve idiopática: remissão completa com bortezomib e dexametasona

### Authors

João Tadeu Damian Souto Filho<sup>1,2</sup>

Jorge Murilo Grillo Monteiro<sup>1</sup>

Inêz Barcellos de Andrade<sup>1,2</sup>

<sup>1</sup> Faculdade de Medicina de Campos (FMC).

<sup>2</sup> Instituto Federal de Educação, Ciência e Tecnologia Fluminense (IFF).

Submitted on: 02/17/2016.

Approved on: 04/25/2016.

### Correspondence to:

João Tadeu Damian Souto Filho.

Faculdade de Medicina de Campos, Campos dos Goytacazes-RJ.

Rua Barão da Lagoa Dourada, nº 320/1202, Centro, Campos dos Goytacazes, Rio de Janeiro, RJ, Brazil.

CEP: 28035-212

E-mail: drjoaotadeu@yahoo.com.br

DOI: 10.5935/0101-2800.20160071

### ABSTRACT

Light chain deposition disease (LCDD) is a rare clinical entity characterized by the deposition of light chain immunoglobulins in different tissues and primarily affects the kidneys, followed by the liver and heart. This disease often manifests as nephrotic syndrome with marked proteinuria and rapid deterioration of renal function. More than 50% of cases are secondary to multiple myeloma or other lymphoproliferative diseases, with a well-established treatment aimed at controlling the underlying disease. In rare cases, there is no detection of an associated hematological disease, referred to as idiopathic LCDD. In these cases, there is no evidence-based consensus on the therapeutic approach, and management is based on the clinical experience of reported cases. Here we report a case of idiopathic LCDD treated with bortezomib and dexamethasone with complete hematologic responses, significant reduction of proteinuria, and improved renal function.

**Keywords:** immunoglobulin light chains; nephrotic syndrome; paraproteins.

### RESUMO

A doença de deposição de cadeia leve (DDCL) é uma entidade clínica rara caracterizada pela deposição de cadeias leves das imunoglobulinas em diferentes tecidos e afeta principalmente os rins, seguido pelo fígado e coração. Manifesta-se frequentemente como síndrome nefrótica com proteinúria marcante e rápida deterioração da função renal. Mais de 50% dos casos são secundários ao mieloma múltiplo ou outras doenças linfoproliferativas, tendo seu tratamento bem estabelecido, voltado para o controle da doença de base. Em casos raros, não há detecção de uma doença hematológica associada, sendo referida como DDCL idiopática. Nestes casos, não há um consenso baseado em evidências sobre a abordagem terapêutica, tendo sua conduta baseada na experiência clínica dos casos relatados. Aqui, nós relatamos um caso de DDCL idiopática tratado com bortezomib e dexametasona atingindo resposta hematológica completa, redução significativa da proteinúria e recuperação da função renal.

**Palavras-chave:** cadeias leves de imunoglobulina; paraproteínas; síndrome nefrótica.

### INTRODUCTION

The light-chain deposition disease (LCDD) belongs to the family of monoclonal immunoglobulin deposition diseases, caused by a dyscrasia underlying plasma cell clones, wherein the light chains of monoclonal immunoglobulins are secreted and deposited in tissues, resulting in varying degrees of organ function loss.<sup>1,2</sup>

More than 50% of cases are secondary to multiple myeloma (MM) or other

lymphoproliferative disease, with a well-established treatment, aimed to control the underlying disease. Several alternatives may be used, and each of them has its own characteristics: corticosteroids, chemotherapy, immunomodulators and autologous hematopoietic stem cell transplantation.<sup>3-11</sup>

However, in the infrequent cases in which there is no detection of an associated hematologic disease, the so-called idiopathic light-chain deposition disease, there is no consensus about its

therapeutic approach and management is based on the experience of reported cases. Thus, this paper aims to report on a case of idiopathic LCDD and discuss the treatment used and its good outcome.

## CASE REPORT

A 55-year old male patient, brown color, married, an oil refining production technician, Brazilian, started about 6 months ago with edema in his lower limbs, dyspnea upon exertion and hypertension of difficult control. During this period, his clinical and laboratory diagnosis was that of nephrotic syndrome, and he was under prednisone 80mg/day; 0.1mg clonidine bid, spironolactone 25mg tid, furosemide 40mg tid, losartan 50 mg bid, captopril 50mg tid and allopurinol 100 mg.

He had no past of diabetes, previous surgery, alcohol consumption and smoking. He had a family history of hypertension (father).

Upon examination, the patient was pallor +/4+, anicteric, acyanotic, afebrile. Cardiovascular system: regular heart rate in two stages with normal heart sounds; blood pressure: 220x120 mm Hg; Heart rate: 86 bpm. Respiratory system: clearly audible breath sounds with crackles in both lung bases and SpO<sub>2</sub>: 94%. Abdomen: flaccid, painless, with no visceromegaly and normal peristalsis. lower limbs: edema ++++/4+ in the leg all the way to the thigh.

Initial laboratory tests: hemoglobin: 10.9 g/dL; hematocrit: 33.5%; leukocytes: 16,200 with a predominance of neutrophils, no left-shift; platelets: 254,000/mm<sup>3</sup>; urea: 164.9 mg/dl; creatinine: 1.98 mg/dL; Uric acid: 9.8 mg/dL; Calcium 8.7 mg/dL; Sodium 140 mEq/L; Potassium: 5.1 mEq/L; erythropoietin: 10.5 U/ml; protein: 5.7 g/dl; albumin: 2.2 g/dl; ferritin: 238 mg/ml; triglycerides: 377 mg/dL; Cholesterol: 309 mg/dL; LDL: 140mg/dl; HDL 94 mg/dL; total bilirubin: 0.56 mg/dL; AST: 25 mg/dL; TGP: 31 mg/dl; Alkaline phosphatase: 55 mg/dl; GGT 28 mg/dL; FAN: 1/80; C3: 102 mg/dL; C4: 18 mg/dl; CH50: 90 U/ml; ESR 20 mm/hr; PCR: 0.08 mg/dL; LDH: 658 U/L; B2 microglobulin: 3.0 mcg/ml.

Negative protein immunofixation; kappa and lambda light-chain dosages: 187 mg/L (normal: 170-370 mg/L) and 106 mg/L (normal is 90 to 210 mg/L) respectively; Dosage free light kappa and lambda chains: 44.2 mg/L (normal: 5.71 to 26.3 mg/L) and 15.9 mg/L (normal: 3.3 to 19.4 mg/L), respectively. Negative for anti-HCV, Anti-HBc, Anti-HBs, HBsAg,

anti-HIV, VDRL, Anti-SM, Anti-DNA, ANCA and rheumatoid factor.

The 24-hour urine evaluation revealed a progressive increase in proteinuria levels: 7.215 mg/24h (6 months before), 8.128 mg/24h (2 months before) and 12,100 mg/24h.

The renal biopsy was performed by needle puncture, with histopathological results indicating 18 glomeruli with increased volume, diffuse hyaline nodular enlargement at a mesangial level with moderate cellularity in this area, distributed mostly on the periphery of the nodules.

We used immunofluorescence to look for antibodies kappa light-chain, with strongly positive result in the glomerular mesangial region and on the periphery of glomerular capillary. Moreover, we found C3 in the mesangium in a granular pattern. Congo red staining was negative. Thus, the diagnostic conclusion was nodular glomerulopathy with kappa light-chains found upon immunofluorescence.

Due to the presence of light-chain deposit-associated nephropathy, there was a need to assess the association with MM, nor looking for light-chain deposition in other organs.

CT scans of the chest, abdomen and pelvis did not show noteworthy changes. Echocardiography and electrocardiography were also normal.

Bone stock with chest, skull, pelvis, upper and lower limbs radiographs, as well as magnetic resonance imaging of the spine showed no evidence of lytic lesions.

Bone marrow biopsy came back normal. We also biopsied his abdominal fat, looking for amyloidosis, and it was negative when stained with Congo red.

Thus, kidney damage with evidence of tissue deposit kappa light-chain concomitant with elevated blood levels of kappa light-chain associated with negative results for MM and amyloidosis were instrumental in establishing the diagnosis of LCDD.

The patient underwent treatment for LCDD with bortezomib and dexamethasone associated with prophylaxis with trimethoprim-sulfamethoxazole and acyclovir, with the goal of preventing infection by *Pneumocystis jirovecii* and herpes viruses, respectively.

During treatment, the patient complained of epigastric pain and appetite loss. We ordered an endoscopy, which showed signs of recent bleeding with gastric ulcer activity, and he was treated with omeprazole.

During the treatment cycles, the patient developed paresthesia in his limbs. Gradually, the patient developed asthenia, dyspnea upon exertion, anemia and hypotension. We suspected of a side effect associated with bortezomib, with peripheral motor and sensory neurological involvements. Thus, we suspended the chemotherapeutic treatment and the antihypertensive agents he was on.

He was submitted to electroneuromyography to confirm the development of peripheral neuropathy, and the result was: chronic, acquired, symmetrical, focal and diffuse myelinic and axonal, sensory and motor, peripheral polyneuropathy. Thus, he was started on gabapentin and analgesics. He improved slowly, but progressively.

Six months after completion of chemotherapy, the patient described significant improvement of his paresthesia, making sporadic use of painkillers. At that time, his creatinine clearance was 101 mL/min and a 24-hour proteinuria was 180 mg/24h, both normal.

The patient evolved favorably, having returned to his professional activities after one year of treatment. After 36 months of follow-up, he is in good health, making use of omeprazole, atorvastatin and calcium. His blood pressure was within normal limits, without signs of edema, remaining with mild residual paresthesia in his limbs.

His laboratory workup is within the normal range, with hemoglobin: 13.3 g/dL, hematocrit: 40.7% urea: 35 mg/dL, creatine: 1.02 mg/dL, creatine clearance of 128.4 mL/min and 24-hour proteinuria: 112 mg/24h.

## DISCUSSION

LCDD is a rare clinical pathologic condition characterized by tissue deposition of non-amyloid immunoglobulin light-chains (kappa or lambda) in granular form, which are not stained by the red Congo.<sup>2</sup> These light-chains will primarily deposit in the kidneys; however, the liver, heart, spleen, small bowel, skin and nervous system may also be affected.<sup>1</sup> Thus, the resulting clinical manifestations depend on what tissues are involved in the deposition of the substance and the consequent organ dysfunction caused.<sup>2</sup>

The mean age of LCDD diagnosis is 58 years, representing a young population when compared to those affected by MM.<sup>1</sup> In addition, men are 2.5 times more affected than women. Approximately 65%

of cases are associated with MM, and 3% to other lymphoproliferative disorders (chronic lymphocytic leukemia). Moreover, 32% of the cases are of idiopathic origin.<sup>3</sup>

The light chains produced are filtered by the glomerulus and reabsorbed in the proximal tubules via receptor-mediated endocytosis; therefore, the kidney becomes an important target for the deposition of these light chains. The kidney lesion is manifested by proteinuria and microscopic hematuria, progressing to decline in function and glomerulonephritis or tubulointerstitial nephritis.

In the liver, often affected in 23% of cases, patients may develop liver failure and portal hypertension. In the heart, there may be an increased heart area, restrictive heart diseases and severe congestive heart failure. In the lungs, there is preferential parenchymal involvement. And finally, in the nervous system, the patient develops neuropathy due to tissue protein deposition.<sup>1,2</sup>

It is a condition that is difficult to diagnose because in 40% of cases the patients may not have a known lymphoproliferative disorder. If the monoclonal light chains are present in the serum and/or urine, the diagnosis becomes easier. However, the LCDD diagnosis can only be confirmed with the immunohistological analysis of affected tissue.<sup>1</sup>

To rule out the differential diagnoses, we need the aspirate and biopsy the bone marrow to rule out MM and/or light-chain amyloidosis. CT and PET scans can also be done to assess systemic diseases.<sup>1,2</sup>

Treatment for Idiopathic LCDD is still controversial, there is no clinical studies or consensus, due to its rarity.<sup>4,6</sup> Treatment depends on the number and nature of the affected organs, and the deposition of different light chains do not seem to affect its clinical evolution.<sup>2</sup>

The prognosis of patients with this clinical entity depends on the age, presence of MM and the presence of light-chain deposition in other organs, apart from the kidney. Therefore, treatment is indicated when there is systemic disease manifestation, severe symptomatic renal dysfunction and when there is concomitant MM activity.<sup>2</sup>

Various treatments have been proposed, all with the aim of suppressing the production of light chains and improve renal function. In the reported case, the treatment employed was bortezomib associated with dexamethasone.

Bortezomib, a proteasome inhibitor, acts in part by inhibiting the action of NFκB, since its activation induces a pro-inflammatory cascade with collagen deposition and changes to the mesangial matrix, which results in pathological changes in the form of glomerulosclerosis.<sup>1,4,5</sup> Thus, the action of this drug is aimed at reducing kidney damage and improving its function.

The association of this drug with dexamethasone significantly reduces proteinuria, promotes rapid hematologic response, and improvements in renal function. Moreover, this association improves blood pressure, reducing the amount of antihypertensive medications administered to the patient.<sup>3,4</sup> This could be demonstrated in our patient. His proteinuria levels reduced from 12,100 mg/24h to 112 mg/24h after treatment, concomitant to antihypertensive suspension and blood pressure normalization.

The main side effect associated with bortezomib was the development of sensory and motor peripheral neuropathy. It is a considerable problem, but manageable in clinical practice, with dose reduction, switching to subcutaneous administration or its entire suspension. Other possible effects include mild and transient orthostatic hypotension, transient elevation of liver enzymes and constipation.<sup>3-6</sup>

Bortezomib and dexamethasone combination is effective for the treatment of patients with LCDD.<sup>3-6</sup> The patient had a deteriorated function at the beginning of treatment, improved in his glomerular filtration, with a drop in his 24h-proteinuria values and normalization of creatinine clearance. In addition, the side effects he developed were those expected for individuals who are treated with bortezomib and dexamethasone.

Should the patient progress poorly, other treatments can be proposed, including the autologous transplantation of hematopoietic stem cells. This treatment produces long-term beneficial outcomes, with a reduction in proteinuria and an increased glomerular filtration rate. However, the side effects found were: bacteremia, diarrhea, mucositis, and death.<sup>5-9</sup>

It is also possible to treat the patients with immunomodulators, including thalidomide and lenalidomide. The combination of this agent with dexamethasone is able to cause a durable hematologic response and improvements to the renal failure.<sup>10,11</sup>

Finally, a treatment of last resort is renal transplantation, which should be reserved for those patients with relative benign course of their disease, whom the production of light chains can be controlled.<sup>1,2</sup>

## CONCLUSION

LCDD is caused by the presence of immunoglobulin light chains in different organs. Among them, the most common are the kidneys, which cause a nephrotic syndrome with marked proteinuria and rapid deterioration of renal function. Most cases are secondary to MM or other lymphoproliferative disease, having a well-established treatment, aimed at controlling the underlying disease.

However, in the infrequent cases in which there is no detection of an associated hematologic disease, called idiopathic LCDD, there is no consensus about its therapeutic approach, and its treatment is based on the experience of reported cases. The reported patient was treated with bortezomib and dexamethasone, but in spite of the side effects, he improved clinically and had resolution of proteinuria and lasting recovery of renal function.

## REFERENCES

1. Jimenez-Zepeda VH. Light chain deposition disease: novel biological insights and treatment advances. *Int J Lab Hematol* 2012;34:347-55.
2. Pozzi C, D'Amico M, Fogazzi GB, Curioni S, Ferrario F, Pasquali S, et al. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis* 2003;42:1154-63. PMID: 14655186 DOI: <http://dx.doi.org/10.1053/j.ajkd.2003.08.040>
3. Gharwan H, Truica CI. Bortezomib-based chemotherapy for light chain deposition disease presenting as acute renal failure. *Med Oncol* 2012;29:1197-201. DOI: <http://dx.doi.org/10.1007/s12032-011-9938-4>
4. Kastritis E, Migkou M, Gavriatopoulou M, Ziropiannis P, Hadjikonstantinou V, Dimopoulos MA. Treatment of light chain deposition disease with bortezomib and dexamethasone. *Haematologica* 2009;94:300-2. PMID: 19066331 DOI:<http://dx.doi.org/10.3324/haematol.13548>
5. Tovar N, Cibeira MT, Rosiñol L, Solé M, de Larrea CF, Escoda L, et al. Bortezomib/dexamethasone followed by autologous stem cell transplantation as front line treatment for light-chain deposition disease. *Eur J Haematol* 2012;89:340-4. PMID: 22690902 DOI:<http://dx.doi.org/10.1111/j.1600-0609.2012.01821.x>
6. Jimenez-Zepeda VH, Trudel S, Winter A, Reece DE, Chen C, Kukreti V. Autologous stem cell transplant for light chain deposition disease: incorporating bortezomib to the induction therapy. *Am J Hematol* 2012;87:822-3. DOI: <http://dx.doi.org/10.1002/ajh.23235>
7. Petrakis I, Stylianou K, Mavroei V, Vardaki E, Stratigis S, Stratakis S, et al. Biopsy-proven resolution of renal light-chain deposition disease after autologous stem cell transplantation. *Nephrol Dial Transplant* 2010;25:2020-3. DOI: <http://dx.doi.org/10.1093/ndt/gfq023>

8. Royer B, Arnulf B, Martinez F, Roy L, Flageul B, Etienne I, et al. High dose chemotherapy in light chain or light and heavy chain deposition disease. *Kidney Int* 2004;65:642-8. PMID: 14717936 DOI: <http://dx.doi.org/10.1111/j.1523-1755.2004.00427.x>
9. Matsuzaki K, Ohsawa I, Nishitani T, Takeda Y, Inoshita H, Ishii M, et al. Marked improvement by high-dose chemotherapy and autologous stem cell transplantation in a case of light chain deposition disease. *J Nephrol* 2011;24:246-9.
10. Fujita H, Hishizawa M, Sakamoto S, Kondo T, Kadowaki N, Ishikawa T, et al. Durable hematological response and improvement of nephrotic syndrome on thalidomide therapy in a patient with refractory light chain deposition disease. *Int J Hematol* 2011;93:673-6. DOI:<http://dx.doi.org/10.1007/s12185-011-0829-4>
11. Gkatzamanidou M, Terpos E, Kastritis E, Dimopoulos MA. Hematologic response and stabilization of renal function in a patient with light chain deposition disease after lenalidomide treatment: a novel therapeutic approach? *Clin Lymphoma Myeloma Leuk* 2014;14:e179-81. DOI: <http://dx.doi.org/10.1016/j.clml.2014.06.002>