Light chain deposition disease:
atypical associations in a rare disease

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◼ ABSTRACT

Light chain deposition disease is a systemic disorder characterized by deposition of monoclonal light chains in various organs. We present a case of a 58-year-old woman who was referred for a nephrology consultation due to worsening renal function and nephrotic range proteinuria. The diagnosis work-up mentioned a plasmatic creatinine of 1.5mg/dL (estimated glomerular filtration rate of 38 mL/min/1.73m2 by MDRD equation), a urinary sediment with microhematuria, a protein/creatinine ratio of 5, a seric and urinary immunoelectrophoresis compatible with a monoclonal gammapathy IgG/Kappa, hypocomplementemia, type II cryoglobulinemia and a pulmonary nodule of irregular shape 15mm in diameter. A renal biopsy was performed and showed a marked expansion of the mesangium with nodules of amorphous material and small outbreaks of tubular atrophy associated with interstitial fibrosis. The nodules were PAS positive and Congo red negative and stained for light chain kappa by immunocytochemistry. Immunofluorescence was negative for IgA, IgG, IgM, C1q and C3c. A diagnosis of light chain deposition disease was made and concomitant multiple myeloma excluded. Treatment was initiated with bortezomib, dexamethasone and thalidomide with complete hematological remission and improvement in renal function. She also showed normalization of the cryoglobulinemia and disappearance of the pulmonary nodule previously detected, despite worsening of cardiac function as a result of the chemotherapy implemented. This clinical case highlights the well-known renal involvement in light chain deposition disease, but also some atypical clinical associations, namely type II cryoglobulinemia and pulmonary nodule disease.

Keywords: Cryoglobulinemia, light chain deposition disease, monoclonal immunoglobulin deposition disease, pulmonary nodule.
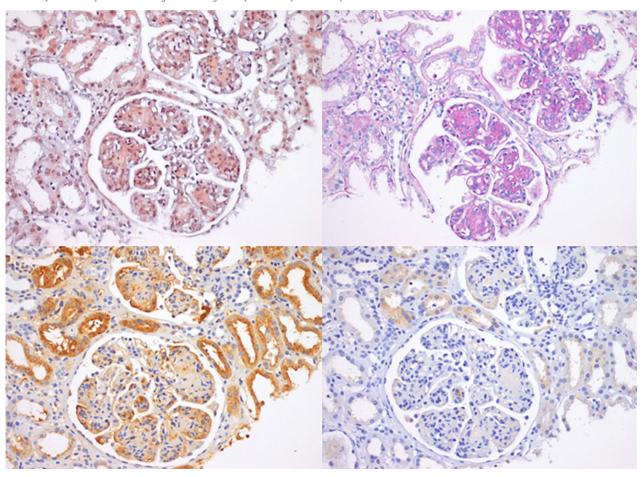
◼ INTRODUCTION

Monoclonal immunoglobulin deposition disease (MIDD) is a group of multisystem disorders characterized by light or heavy chains deposition of monoclonal immunoglobulins in various organs[1,2]. The most commonly diagnosed MIDD is light chain deposition disease (LCDD), followed by heavy chain deposition disease and light and heavy chain deposition disease. LCDD is a rare disease with a male predominance and a median age at diagnosis of 58 years old. It is usually associated with monoclonal gammopathies of undetermined significance in 17% and with multiple myeloma (MM) in 58% of patients[2,4-5]. In LCDD there is a single clone of plasma cells responsible for the overproduction of kappa, in the majority of cases, or sometimes lambda light chains[3]. Clinical manifestations vary, depending on which organs are predominantly involved, with the kidney one of the most commonly affected. This is explained by the fact that light chains (LCs) are filtered

by the glomeruli, reabsorbed in proximal tubules by receptor mediated endocytosis, and degraded in tubular cells by lysosomal enzymes. The clinical scenario might be one of a glomerulopathy, including rapidly progressive glomerulonephritis or an acute tubulointerstitial nephritis[1,4] revealed by renal lesion, hypertension, microhematuria, proteinuria and more rarely renal tubular acidosis. The characteristic pathologic features of renal LCDD include nodular sclerosing glomerulopathy by light microscopy; diffuse linear staining of glomerular and tubular basement membranes for a single light chain by immunofluorescence; and nonfibrillar, 'powdery' electron-dense deposits in basal membranes detected by electron microscopy[6]. Symptomatic extrarenal deposition is rare[2] but hepatic, cardiac, pulmonary[14] and neural deposits have been documented. The clinical course of an untreated disease is one of inexorably progressive chronic kidney disease (CKD) and death. In light of the scarcity of published studies, the treatment is based in chemoterapy and autologous stem cell transplant[1,5-10] in selected cases.

■ CASE REPORT

A 58-year-old Caucasian woman with an history of hypertension controlled with an ACEI, a thiazide and a beta-blocker with no clinically known micro or macrovascular involvement, active tabagism with chronic bronchitis and a mitral valve rheumatic stenosis was referred for a nephrology consultation due to worsening renal function with a plasmatic creatinine (pCr) of 1.3mg/dL (estimated glomerular filtration rate

Figure 1

Renal biopsy. Top figures, left to right: Congo red negative staining and PAS positive staining; bottom figures, left to right: Kappa light chain positive by immunocytochemistry and Lambda light chain negative by immunocytochemistry.

(GFR) of 42mL/min/1.73m2 by MDRD-4 equation) and nephrotic range proteinuria (3537mg in a 24h urine specimen). The work-up showed a serum creatinine of 1.5mg/dL (estimated GFR of 38 mL/min/1.73m2 by MDRD-4 equation), a urinary sediment with micro-hematuria, a protein/creatinine ratio of 5, a protein determination of 4.2g in a 24h urine specimen (with 72% albumin), a serum albumin of 3.3 g/dL, and a total protein of 5.2g/dL. A kidney ultrasound showed normal-sized kidneys with normal parenchyma and no signs of lithiasis or obstructive uropathy. A seric electrophoresis showed a gamma spike; seric and urinary immunoelectrophoresis were compatible with a monoclonal gammopathy IgG/Kappa, and the serum kappa/lambda ratio was 1.53. Serum free light chains determination was not available in our institution. She had normal liver-function tests, an unremarkable complete blood count, and unremarkable peripheral blood immunophenotyping by flow cytometry. The serological work-up showed normal immunoglobulin levels, hypocomplementemia (C3 of 63mg/dL (N 83-193) and C4 of 13.3mg/dL (N 15-57)) and a type II cryoglobulinemia (82mcg/mL (N<20); IgG with poly-clonal features and a monoclonal fraction IgG/Kappa without rheumatoid activity). ANCAs, ANAs, ENAs, rheumatoid factor, anti-dsDNA, anti-GBM were nega-tive and she also had negative serology for HIV and HCV (including cryocrit negative for HCV antibody). A prior HBV infection was detected (anti-HBs and anti--HBc positives and HBsAg negative). Viral load was not measured. A transthoracic echocardiography showed preserved systolic function, normal sized chambers without hypertrophy apart from the already documented moderate mitral insufficiency; electro-myography study was also normal. A pulmonary nod-ule of irregular shape 15mm in diameter, not present one year prior in a similar exam, was observed in a thorax CT. A renal biopsy was performed (Figure 1): glomeruli showed a marked expansion of the mesan-gium frequently with nodules of amorphous material; small outbreaks of tubular atrophy and interstitial fibrosis were also present. Glomerular nodules were PAS positive, Congo red negative and displayed restric-tion for kappa light chain by immunocytochemistry, and were negative for lambda light chain. Immuno-fluorescence microscopy was negative for IgA, IgG, IgM, C1q and C3c. A diagnosis of LCDD was performed with concomitant exclusion of an MM by bone mar-row aspirate and biopsy with immunophenotyping showing <1% plasmocytes, normal cellularity and no identifiable bony or extramedullary plasmacytoma by means of computed tomography (CT). Treatment was started with bortezomib, dexamethasone and thalidomide for six cycles with complete hematological remission, resolution of the cryoglobulinemia and hypocomplementemia and disappearance of the pul-monary nodule. Despite that, there was progression to CKD stage 4/A1. Due to chemotherapy there was also worsening of cardiac function with development of a dilated cardiomyopathy with global hypokinesis and a marked ventricular function depression of 28% of non- ischemic etiology as suggested by the cardiac MRI and also a peripheral neuropathy in relation with thalidomide use.

DISCUSSION

In the case presented, the clinical scenario was pre-dominantly a glomerulopathy, with hematuria and a nephrotic range proteinuria. With the results of the serum and urine immunoelectrophoresis and the pre-dominance of kappa light chains, the diagnosis of an LCDD was the most likely, and was later histologically confirmed. Due to the high co-association with MM[2,4-5] this pathology was excluded. Our case is exceptional for two particularities – the association with cryoglo-bulinemia type II and with pulmonary nodular disease. Regarding the cryoglobulinemia, two clinical scenarios can be postulated: 1) the patient could have had an essential mixed cryoglobulinemia of unknown etiology that could have been clinically silent[12,13] until the development of the LCDD; or 2) it could be an unusual manifestation of the LCDD. The last is the most prob-able cause, as the histological pattern was not one of a renal manifestation of cryoglobulinemia, and mainly because with chemotherapy, there was resolution of the cryoglobulinemia. Pulmonary nodular disease is a described, but still unusual, association with LCDD[14]. LCDD rarely involves the respiratory system, mainly the pulmonary parenchyma and the bronchi, and sometimes the interstititium, in the form of a nodular or diffuse pattern[14]. In our case the nodule formation was already extensively studied in a pulmonology con-sultation, the previous year. The resolution of the pul-monary image with the treatment of the LCDD suggests a possible, but still unproven due to the lack of a nodu-lar biopsy, association with the LCDD. In relation to the treatment option, a bortezomib-based scheme is possibly the choice with the best outcomes to achieve a complete (CR) or very good partial response (VGPR)[1,2]. Aggressive chemotherapy should be attemped even in patients with advanced renal diseases as it has been demonstrated that an improvement in renal function could be achieved by the end of the first year if a clonal

response can be sustained[1]. Also, following the same studies, its unquestionable that after achievement of a CR/VGPR, the next step is autologous stem cell transplant (ASCT)[1,15-16]. While the best choice for a chemotherapy scheme, proteasome inhibitors can induce cardiotoxicity[17]. In our case the echocardiography changes were concomitant with the chemotherapy with confirmation on the cardiac MRI, which showed a dilated cardiomyopathy with a global hypokinesis and marked ventricular function depression, the typical pattern in cases of chemotherapy induced cardiotoxicity. Thalidomide could also have been an adjuvant, but is typically associated with sinus node dysfunction, bradyarrhythmias and heart block[17]. Even so, the incidence of heart failure under bortezomib is relatively low (up to 4%), with meta-analyses and other investigations showing conflicting results with regards to this risk, apart from that it could be exacerbated by the concomitant use of steroids[19,20]. In the absence of a known cardiac condition with clinical heart failure, as was the case, it is the best choice for chemotherapy. Proving this association is the slight improvement in the cardiac function in the latest transthoracic echocardiography. Cardiac dysfunction is the reason for not performing ASCT at this time. Peripheral neuropathy that could have been induced by both thalidomide and bortezomib, as it also improved at the end of treatment. In conclusion, LCDD is a systemic disease with a poor outcome, if not detected and treated aggressively early in its course. The differential diagnosis is vast, as its clinical manifestations and associations can be, with kidney biopsy playing a vital role in its differentiation.

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