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# Renal failure due to light chain deposition disease

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## CASE REPORT

A 64 year-old woman with a history of multinodular goiter, osteoporosis and duodenal ulcer referred asthenia and dyspnea for several months. The initial laboratory investigations disclosed Hb value of 9 g/dL. The patient was referred to the Hematology Department, where a normocytic anemia with low blood production, as well as total protein levels of 8.2 g/dL and albumin levels of 4.2 g/dL were detected. An IgG Kappa peak was seen by serum immunofixation. The bone marrow aspirate revealed diffuse plasmacytosis and an immunophenotype with a mainly monoclonal component, with aberrant characteristics similar to myeloma cells. According to percentage of plasmocytes the condition was classified as monoclonal gammopathy of undetermined significance. The creatinine value was 1.6 mg/dL and creatinine clearance was 23 mL/min, and the patient was referred to Nephrology. Antinuclear, anti-mitochondrial and anti-cytoplasmic antibodies were negative. A proteinuria of 352 mg/24 h was found with no monoclonal peaks on urine immunofixation. On renal ultrasound the kidneys measured 9.5 and 10.5 cm and the corticomedullary area was spared. Treatment was initiated with oral iron and erythropoietin.

In the following months high blood pressure developed with progressive worsening of renal function, creatinine levels reaching 4.7 mg/dL. A subcutaneous cellular tissue biopsy was negative for Congo red stain. The echocardiography showed diastolic dysfunction without left ventricular hypertrophy. Proteinuria reached 800 mg/24 h and immunofixation disclosed monoclonal IgG kappa type and albumin traces.

A percutaneous renal biopsy was performed and the sample was analyzed by means of conventional light microscopy, immunohistochemistry and direct immunofluorescence on 3 µm slices obtained with the cryostatic microtome. Light microscopy showed a globally distorted structure because of severe glomerular involvement and chronic tubulo-interstitial nephropathy, moderate inflammatory infiltrate with lymphoid predominance and atrophic tubular groups with sclerosed glomeruli. A total of ten glomeruli could be identified, three of them were sclerosed, while the rest showed lobule-like clews, marked diffuse mesangial enlargement, with a nodular tendency (figs. 1 and 2), a cellular component, PAS+ material and reticulate appearance. PAS+ material could also be observed within the Bowman's capsule, as well as in the tubular basement membrane, in an evident zone, that with the Masson's trichromic stain appeared to be fuchsinophilic. There was no material that stained with Congo red technique. In the medulla a vast interstitial deposition of PAS positive material could be seen.

The following anti-sera were applied for the direct immunofluorescence technique (FITC): anti-IgG, anti-IgA, anti-IgM, anti-C3, anti-C1q, anti-kappa chains and anti-lambda chains. Two glomeruli could be seen in each slice. Of note was the fixation of the anti-kappa chains serum in glomerular and tubular basement membrane and Bowman's capsule, including the interstitial material seen in the medulla (fig. 3). The immunohistochemistry for kappa and lambda chains yielded similar results as those seen with immunofluorescence (fig. 4).

The pathological diagnosis was kappa chains deposition-induced nephropathy and chronic tubulo-interstitial nephropathy.

## EVOLUTION

After the biopsy, renal function went on worsening until the patient required renal replacement therapy. The patient is currently on chronic hemodialysis. Treatment with melphalan and prednisone was initiated and the monoclonal IgG peak could be reduced. She always needed frequent transfusion therapy.

## DISCUSSION

Dysproteinemic disorders are characterized by immunoglobulin synthesis by clones of B lymphocytes. They are associated to different forms of renal disease, like nephropathy due to Ig deposition or precipitation. In patients with light chains deposition disease, the typically Kappa Ig fragments accumulate in a disorganized granular manner, different from the crystalline deposition observed in «myeloma kidney», the fibrillary deposition of amyloidosis and the microtubular deposition of immunotactoid glomerulopathy. The different structural characteristics are responsible for the different clinical pictures. For

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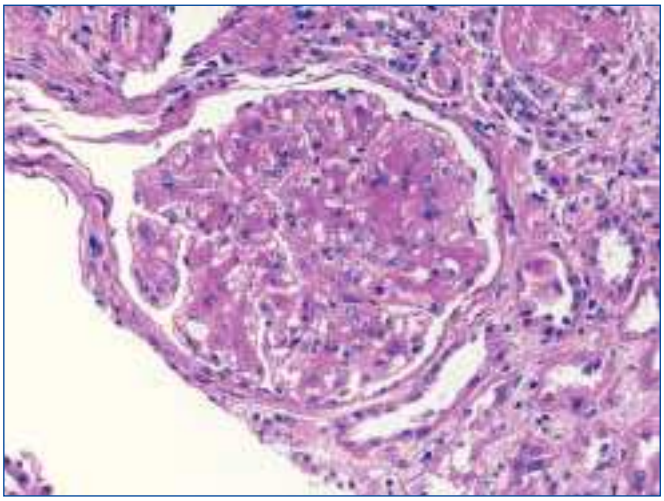

**Figure 1.** Glomerulus with a pattern of nodular glomerulosclerosis and diffuse mesangial enlargement (H & E).

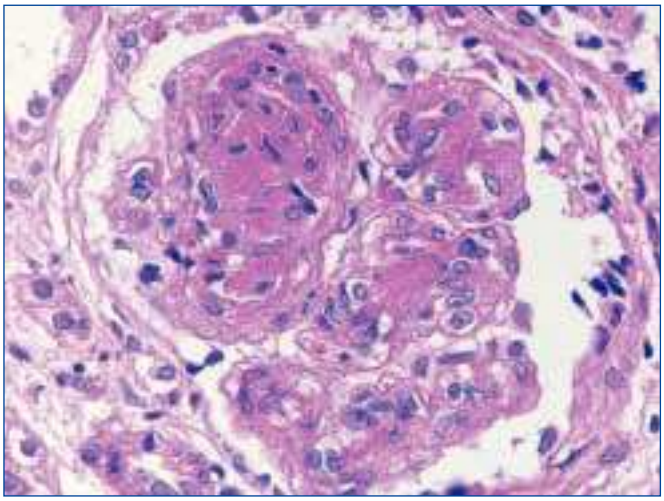

**Figure 2.** Glomerulus with a pattern of nodular glomerulosclerosis and diffuse mesangial enlargement (H & E).

example, the myeloma kidney progresses rapidly to renal failure, even with acute flares, while the conditions with predominantly mesangial depositions lead to clinical pictures like nephrotic syndrome.[1]

The factors determining the formation of granular or fibrillary tissue deposition are not clearly understood. If light chains from affected patients are infused into mice a similar renal lesion is produced, like that in patients. That suggests that the biochemical characteristics of the protein are relevant.[2] Likewise, some *in vitro* studies indicate that the amino acid composition or the net protein charge could determine the deposition formation.[3] For example, it was initially observed that in the majority of the patients the chains were longer or shorter as usual and that was associated to a greater tendency to precipitate. In recent studies, the investigation of chains which were not initially detected showed that they were N-glycosilated, which increases their ability to precipitate and makes them difficult to detect in serum.[4] Moreover, the sequencing studies reveal that most of the abnormalities are localized within the molecular area involved in antigen-binding and so it is possible that the first step in deposition formation could be the interaction with a foreign component acting as an antigen.[5] The present case is an especially illustrative example of the importance of the protein type, as the apparently low grade of abnormal protein synthesis and urine elimination is associated to severe, rapid and characteristic renal disease. Renal involvement in cases of light chains deposition disease is constant, and most patients develop renal failure and proteinuria.[6] Up to a 55% of cases present nephrotic syndrome and in those patients with proteinuria lower than 1 g/d the main clinical picture is a tubulointerstitial syndrome.[7] Hematuria can be detected in up to a 40% of the cases. The evolution to end-stage is usually rapid and frequently similar between patients with varying degrees of proteinuria. Other organs are less frequently affected than with amyloidosis, hepatomegaly and hepatic dysfunction being possible and seldom heart involvement is seldom encountered. The disease can be associated to other conditions like lymphoma, leukemia, Waldenström's macroglobulinemia or multiple myeloma, which are diagnosed in up to 50% of the cases. In 10%-15% of patients monoclonal immunoglobulin is not detected either in blood or in urine. That is probably not due to a lack of secretion, but to rapid post-synthesis tissue deposition or protein degradation.

The analysis of the renal biopsy samples by means of light microscopy always shows the deposition of eosinophilic PAS positive material in the outer part of the basement membrane. Glomerular lesions are more heterogeneous, being most characteristic the nodular glomerulosclerosis. Mesangial nodules consist of PAS-positive Congo red-negative material, which is accompanied with hypercellularity in most cases. In the early stages or in case of mild involvement, it is possible to find only an increase in mesangial matrix and mild hypercellularity, with mild enlargement of the basement membranes. In advanced disease a marked interstitial fibrosis can also be seen including depositions, independent of the tubular lesions.[8] Besides depositions related to the basement membrane of arteries, arterioles and peritubular capillaries can be observed. The differential diagnosis must be made with diabetic nodular glomerulosclerosis. In this condition Kimmelstiel-Wilson's nodules are more frequently localized in the periphery of the glomerulus, and exudative lesions and hyalinosis can also be observed within the efferent arteries. The differential diagnosis with amyloidotic nephropathy is made by means of Congo red stain, which is negative in light chains depositions.

The immunofluorescence technique shows the fixation of the anti-light chains anti-serum, mainly of the kappa type, along the tubular basement membranes. Glomerular depositions are extensively observed in basement membranes and less markedly in the nodules themselves and the fixation is typically weaker than that on the tubules. In patients without nodular lesions mesangial involvement can be appreciated.

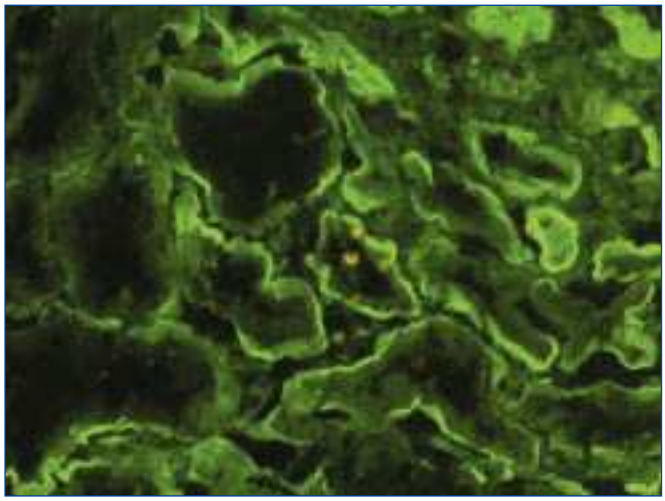

**Figure 3.** Fixation of anti-κ chains in glomerular and tubular basement membrane and in Bowman's capsule (anti-κ chains direct IF).

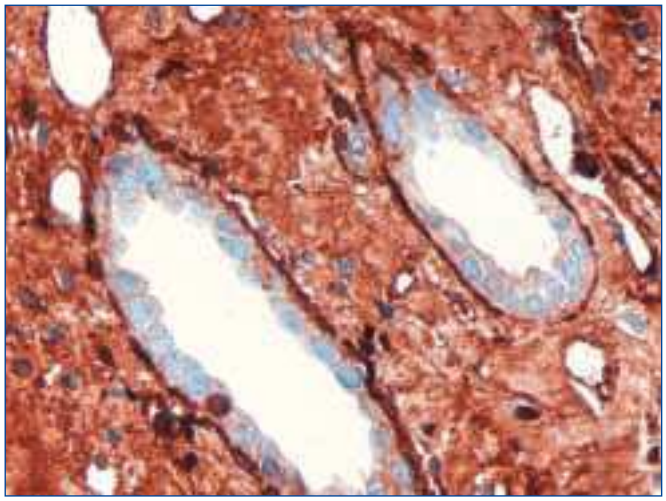

**Figure 4.** Fixation of anti-κ chains within tubular basement membrane (IHQ).

Lineal depositions of light chains within the basement membrane of Bowman's capsule can also be observed and they are always present in vascular walls. Immunofluorescence is strongly positive comparing to that of amyloidosis, as the Ig fraction that forms the depositions is typically the constant region.[1]

On electronic microscopy granular depositions of electron dense material along the outer side of the basement membranes and in mesangial nodules are observed. Basement membranes are preserved.

Disease evolution is variable since extrarenal deposition may vary from completely asymptomatic to severe organic dysfunction. In published series, survival from the time of diagnosis can vary from 1 month to 10 years. The prognosis is worse in patients with associated myeloma and greater extrarenal involvement.

The treatment is directed to diminishing immunoglobulin production with chemotherapy to eliminate the plasma cells clone that produces the monoclonal protein. In young patients bone marrow transplantation is concomitantly performed. In some cases, it was not only observed a disappearance of immunoglobulin in blood an urine, but also the regression of the mesangial nodular lesions and of the light chains depositions. That supports an aggressive approach in patients with severe visceral involvement.[9] Some cases are reported in which renal function notably improved, even after initiating renal replacement therapy. After transplantation the disease always recurs. For this reason the transplantation is not indicated unless complete hematologic remission is achieved.[10]

## QUESTIONS

**Dr. Rivera (General Hospital of Ciudad Real).** *Patients diagnosed with monoclonal gammopathy of undetermined significance and renal involvement with diminution of glomerular filtration rate and mild proteinuria are frequently encountered. Most patients are of advanced age and have concomitant conditions like type 2 diabetes mellitus or arteriosclerosis, which are also associated to renal involvement. The clinical picture is then diagnosed as nephroangiosclerosis or diabetic nephropathy. In this setting, are the results from blood and urine immunofixation indicative of the presence of a light chain nephropathy? What kind of immunoglobulin or light chain is most nephrotoxic?*

**R**: The presence of light chains, mainly kappa type in immunofixation (keeping in mind that they are not detected in 10-15% of the cases) points out the presence of this nephropathy, especially if nephroangiosclerosis is accompanied by unexplained proteinuria, or if there is a rapid progression of diabetic nephropathy.

The kappa isotype is mostly identified, although the nephrotoxicity seems to be determined by the deposition conformation. Nevertheless different mutations in Ig chains can be involved in the type of deposition. It was also observed that in the case of amyloidosis different variable regions of lambda chain could determine the affinity to the different tissues.[11]

**Dr. Poveda (Hospital of Bellvitge. Barcelona).** *Your case clearly illustrates the poor prognosis of light chains nephropathy. On the other hand some authors point out that good results may be achieved with chemotherapy if early applied. That speaks for an early diagnosis. To your opinion, which are the indications of a renal biopsy in patients with monoclonal gammopathy and renal involvement?*

**R**: The prevalence of the gammopathy of undetermined significance in patients older than 70 years is 3%, and this percentage increases with age. Concomitant morbidity, which can explain the renal disease, is also very frequent, as we have already commented. So, we think that it is not efficacious to schedule a biopsy in all cases. We think the indication should be limited to those patients in whom no other causes of renal failure can be found or if an unexplained

worsening of renal function develops. It would be interesting if in the future the conformational characteristics of the proteins responsible for the pathogenesis could be detected.

**Dr. Julia Blanco (San Carlos Clinic University Hospital. Madrid).** *The glomeruli with silver methenamine stain are strongly positive. Have you seen something similar in other cases of light chain disease? In patients seen at the Clinic University Hospital of Madrid, the mesangial nodules, as well as the enlarged tubular basement membranes are strongly argentophilic. However in some books of Nephropathology, such as Tisher–Brenner's textbook of Renal Pathology the negativity of glomerular depositions with silver technique is established as a dogma. What do you think about?*

**R**: In fact, the positivity has also been described in similar cases. I think that the silver technique is useful, but the results must be interpreted with caution, probably taking into account the time course and the different compositions of the chains with different affinity for the silver stains.

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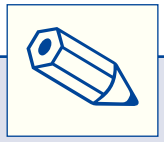

## THE EDITOR'S NOTE

The Jury considered this case as the best presentation of a clinical case at the last meeting of the 2007 Nephropathology Club.