Non-amyloid deposits glomerulopathy with multiple myeloma; a rare presentation

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Keywords: Multiple myeloma, Non-amyloid deposits, Glomerulopathy

Abstract
Renal complications in multiple myeloma are common. The occurrence of non-amyloid deposits glomerulopathy is rare. We report an exceptional non-amyloid deposits glomerulopathy in a patient followed for multiple myeloma in complete remission. A 70-year-old male patient, followed for lambda light chains multiple myeloma, and treated according to the protocol “Alexanian” with a complete remission at the end of treatment. After one year of follow-up, a deep pure nephrotic syndrome occurred. Renal biopsy was then conducted. It included 10 glomeruli, all with pseudo-amyloid deposits, amorphous and stifling tuft. Congo-red was negative. Immunofluorescence objectified a glomerular and mesangial intense, diffuse and global IgG deposits. The electron microscopic examination was not conducted. Kidney damage in multiple myeloma include tubulointerstitial nephropathy and immunoglobulin glomerulopathy, which amyloidosis deposits and Randall syndrome. The clinic context, as well as the appearance in optical microscopy of renal fragment moving towards renal amyloidosis. Paradoxically, the Congo-red staining was negative, in favor to a non-amyloid deposits glomerulopathy. An electron microscopic examination is needed to highlight the fibrillar or microtubular deposits. The occurrence of non-amyloid deposits glomerulopathy in multiple myeloma is exceptional. The study by light microscopy, immunofluorescence and electron microscopy especially makes it easy to diagnose.

Introduction
Renal involvement in multiple myeloma is common and it is an important prognostic factor. It is represented mainly, when it is manifested by a tubular syndrome, by the myeloma tubulopathy or Fanconi syndrome. When it is glomerular involvement, it is most often AL-amyloidosis, or syndrome of monoclonal immunoglobulin deposits (MDIM) initially known under the term of “Randall syndrome” or exceptionally non-amyloid deposits glomerulopathy. It is consisting on two entities; the pseudo-amyloid fibrillar glomerulopathy and micro-tubular deposits glomerulopathy. We report an exceptional non-amyloid deposits glomerulopathy occurred to a patient followed for light chains lambda multiple myeloma classified stage IIIA according to the classification of Durie and Salmon in complete remission after a treatment according to the “Alexanian” protocol (1,2).

Case Report
A 70-year-old woman, followed and treated

Key point
Renal complications in multiple myeloma are common. The occurrence of non-amyloid deposits glomerulopathy is rare. The occurrence of non-amyloid deposits glomerulopathy in multiple myeloma is exceptional, however, the study by light microscopy, immunofluorescence and electron microscopy especially makes it easy to diagnose.

Renal complications in multiple myeloma are common. The occurrence of non-amyloid deposits glomerulopathy is rare. We report an exceptional non-amyloid deposits glomerulopathy in a patient followed for multiple myeloma in complete remission. A 70-year-old male patient, followed for lambda light chains multiple myeloma, and treated according to the protocol “Alexanian” with a complete remission at the end of treatment. After one year of follow-up, a deep pure nephrotic syndrome occurred. Renal biopsy was then conducted. It included 10 glomeruli, all with pseudo-amyloid deposits, amorphous and stifling tuft. Congo-red was negative. Immunofluorescence objectified a glomerular and mesangial intense, diffuse and global IgG deposits. The electron microscopic examination was not conducted. Kidney damage in multiple myeloma include tubulointerstitial nephropathy and immunoglobulin glomerulopathy, which amyloidosis deposits and Randall syndrome. The clinic context, as well as the appearance in optical microscopy of renal fragment moving towards renal amyloidosis. Paradoxically, the Congo-red staining was negative, in favor to a non-amyloid deposits glomerulopathy. An electron microscopic examination is needed to highlight the fibrillar or microtubular deposits. The occurrence of non-amyloid deposits glomerulopathy in multiple myeloma is exceptional. The study by light microscopy, immunofluorescence and electron microscopy especially makes it easy to diagnose.

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A 70-year-old woman, followed and treated

for lambda light chains multiple myeloma. The diagnosis was made following criteria developed by the South West Oncology Group; 50% of bone marrow involved by plasma cells, a monoclonal peak in the region of gamma globulin with lambda bands in serum immunofixation, Bence Jones proteinuria consisting on lambda light chains 2.5 g/day and multiple osteolytic lesions. The tumor mass was high. Plasma hemoglobin; 7 g/dL, corrected serum calcium; 140 mg/dL and the monoclonal IgG immunoglobulin level exceeded 70 g/L. Renal func-
tion was preserved. Multiple myeloma was classified stage IIIA according to Durie and Salmon classification, and stage 3 of the International Staging System classification (ISS) since β2-microglobulin was 17 mg/L. It should be noted also that there was no extra-renal signs (including skin), and cryoglobulinemia was not existed. Treatment according to the p Alexanian protocol was established for two reasons; the age of the patient and the autograft was not possible. The evolution was marked at the end of treatment by a complete remission of multiple myeloma. However, the patient consulted again a year later for a significant edema syndrome associated with a pure and deep nephrotic syndrome. Renal biopsy was then conducted. It included 10 glomeruli, which consisted the PAS positive mesangial pseudo-amyloid deposits, without deposits in tubular membranes. Congo-red was negative. Immunofluorescence objectified glomerular mesangial deposits of IgG, intense diffuse and global. The electron microscopic examination could not be performed (Tables 1 and 2).

**Discussion**

The glomerulus is a capillary vascular structure, which is continuously exposed to plasma proteins. Renal plasma flow (glomerular) represents 20% of total plasma flow. As a result, the glomeruli is one of the first structures of the body in which the abnormal deposit or those who have a special affinity for the constituents of the capillary walls, especially basement membranes (2,3) proteins. Renal involvement in multiple myeloma is more common, it could be myeloma tubulopathy or Fanconi syndrome when it is manifested by a tubular syndrome, and when the presentation of nephropathy is glomerular, then it would be, on the one hand, AL amyloidosis or non-amyloid deposits glomerulopathy, or on the other hand, the disease of monoclonal immunoglobulin deposition (MDIM) originally known under the term of “Randall syndrome” (4-6). The spectrum of glomerular diseases characterized by the deposition or precipitation of monoclonal immunoglobulin components has grown considerably. These diseases can be classified into two categories by the scanning electron microscope. The first category is defined by organized fibrillar deposits (mainly observed in AL-amyloidosis or in non-amyloid deposits glomerulopathy), or microtubular deposits (renal cryoglobulinemia and immunotactoid glomerulopathy) (2). The second category is characterized by granular, electron-dense and unorganized deposits. These deposits are located in the basement membrane, mainly those vascular, on most of the tissues. They define MDIM syndrome or Randall (2).

Thus, the diagnosis of pseudo-amyloid fibrillary or micro-tubular glomerulopathy requires an ultra-structural study of renal biopsy, but it is less common. Its incidence is certainly underestimated (less than 1% of biopsies performed on native kidneys) (2).

Renal presentation of AL-amyloidosis in myeloma is not different from that of non-amyloid deposits glomerulopathy (NADG). They are manifested by a non-selective glomerular proteinuria in nephrotic rank. However, microscopic hematuria, hypertension and progression to chronic renal failure are specific of NADG (2). The AL-amyloidosis is often responsible for periocular and skin purpura, a macroglossia, a carpal tunnel syndrome, peripheral and autonomic neuropathy, a restrictive cardiomyopathy and hepatomegaly, however extra-renal damage in NADG is exceptional (3,6,7). Renal presentation of our patient approached over that of AL amyloidosis with nephrotic proteinuria without hematuria or hypertension or renal failure. However, there was no extra-renal signs.

In light microscopy, the amyloid deposits are extracellular, amorphous, eosinophilic, slightly PAS positive, especially Congo-red positive with birefringence and yellow-green dichroism in polarized light. In electron microscopy, these deposits consists on straight fibrils, unconnected, which their diameter is between 8 to 10 nm, without individualized central light. These fibrils are arranged in all directions, in “lots of pins” and form deposits of varying density. These deposits consist of monoclonal immunoglobulins most often lambda light chains (kappa/lambda = 1/4) (3,5). The pseudo-amyloid deposits are mesangial, eosinophilic, PAS positive, Congo red negative deposits, consisting mainly of IgG. In electron microscopy, they are made, in case of fibrillary glomerulopathy, of arranged and straight fibers evoking amyloidosis (6-10). They are considered pseudo-amyloidosis deposits, since Congo-red light microscopy is negative and in electron microscopy, the fibrils have a larger diameter (15 to 20 nm). If it is micro-tubular deposits glomerulopathy, the appearance in light microscopy is identical. At the opposite of glo-

### Table 1. Deposits of monoclonal immunoglobulins

<table>
<thead>
<tr>
<th>Fibrillar deposits</th>
<th>Granular deposits (Congo-red negative)</th>
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<tbody>
<tr>
<td>Congo-red positive</td>
<td>Congo-red negative</td>
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<tr>
<td>AL-amyloidosis</td>
<td>Pseudo-amyloid</td>
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LCDD: deposits of light chain disease; HCDD: deposits of heavy chain disease light chains; LHCD: deposits of light and heavy chain disease.

### Table 2. Renal disease in multiple myeloma

<table>
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<tr>
<th>Glomerular syndrome</th>
<th>Immunoglobulin deposition disease (MDIM)</th>
<th>Tubular syndrome</th>
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<tbody>
<tr>
<td>Organized deposits</td>
<td>Unorganized deposits (RC-)</td>
<td>Myeloma tubulopathy</td>
</tr>
<tr>
<td>RC +</td>
<td>RC -</td>
<td>Fanconi Syndrome</td>
</tr>
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<td>AL Amyloidosis</td>
<td>Randall</td>
<td></td>
</tr>
<tr>
<td>Microtubular deposits GP</td>
<td>Fibrillar deposits GP</td>
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</table>
Non-amyloid glomerulopathy

merular lesions in cryoglobulinemia, no real thrombus or significant influx of macrophages, or evidence of vasculitis associated intra- or extra-renal was detected (9-11). In electron microscopy, the deposits consist of microtubules frequently straight, with a prominent central lumen. Their diameter is varying from 10 to 50 nm. And finally, the deposits in the Randall syndrome are different. They are dense, granular and osmiophilic. In our patient, the deposits were typically pseudo-amyloid, amorphous, eosinophilic and Congo-red negative. In immunofluorescence, there was only deposits of glomerular mesangial, intense, diffuse and global IgG. The ultra-structural study has not been made.

It should be remembered that, only the heavy chemotherapy followed by autologous circulating hematopoietic cells may allow remission of AL-amyloidosis (9-12).

Conclusion
The occurrence of non-amyloid deposits glomerulopathy in multiple myeloma is exceptional. The study by light microscopy, immunofluorescence and electron microscopy makes it easy to diagnose. The prognosis is unfortunate and evolution is inevitably to chronic renal failure. However, it is less pejorative in case of recurrence after renal transplantation.

Authors’ contribution
All authors wrote the paper equally.

Conflicts of interest
The authors declared no competing interests.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support
None.

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