Renal involvement in non-malignant IgM gammopathy

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**Keywords:** gammopathy; IgM nephropathy; monoclonal

**Introduction**

Renal involvement is observed frequently in association with malignant gammopathies, mainly those related to light chain deposition [1]. Nevertheless, light chain deposition renal disease has also been described in non-malignant monoclonal gammopathy, namely in IgG or IgA plasma cell dyscrasia [2,3].

Renal involvement in IgM monoclonal disorders is traditionally described in patients with malignant disease (Waldenström’s macroglobulinaemia) that includes the deposition of monoclonal IgM and light chains on mesangium and glomerular capillary wall [4–6].

IgM monoclonal gammopathy without malignant criteria can be found in asymptomatic patients or associated with polyneuropathic disease, but renal involvement has rarely been described in this clinical setting [7,8].

We report the case of a patient with non-malignant IgM/κ gammopathy, who developed nephrotic proteinuria and progressive renal failure in association with renal deposition of IgM and κ light chains.

**Case**

A 48-year-old man was admitted to our department after detection, in an ordinary analysis, of microhaematuria, proteinuria and renal failure. He had given up smoking 2 years previously. The patient had nephritic colic due to uric lithiasis and hypercholesterolaemia controlled by diet.

Results of the physical examination were normal, including for the neurological system. The laboratory blood test showed: Urea: 12.7 mmol/l, creatinine: 252 μmol/l, sodium: 143 mmol/l, potassium: 5.2 mmol/l, albumin: 38 g/l, uric acid: 345 μmol/l, γ-glutamyltransferase: 0.29 ukat/l, alkaline phosphatase: 1.9 ukat/l, and calcium: 2.27 mmol/l. Erythrocytes were 4.73 × 10¹²/l; haemoglobin, 13.7 g/dl; and leucocytes, 10.85 × 10⁹/l with normal differential count. Platelet count and coagulation test were normal. Red cells in urine sediment were 76 000/min. Proteinuria in 24 h was 4–5 g. Serum antibody search for human immunodeficiency virus, hepatitis C virus, hepatitis B virus and lues were negative. Serum complement fractions were normal. Search for rheumatoid factor, cryoglobulin, anti-nuclear antibodies and antineutrophil cytoplasmic antibodies in serum were negative in several times. Serum immunoglobulin had high IgM (445 mg/dl) and low IgG and IgA levels (465 and 57 mg/dl, respectively). Serum and urine electrophoresis showed no peaks in routine register. Serum and urine immunofixation revealed a monoclonal component consisting of μ and κ chains. Bone marrow aspiration and biopsy were normocellular. There was no evidence of clonal lymphoproliferative disease. Immunophenotype of B-cells showed polyclonality.

Chest and abdominal computerized tomography (CT scans) ruled out organomegaly and lymphadenopathic images. Skeletal radiographic survey was normal. Optic funduscopy showed no signs of hyperviscosity.

Light-microscope examination of the renal biopsy revealed 23 glomeruli with expansion of mesangial matrix and focal proliferation of mesangial cells. There were crescent lesions in 40% of glomeruli. Focal and segmentary double-contoured capillary wall was observed. Congo red staining was negative. Some tubular atrophy and interstitial infiltrate consisting of scattered lymphocytes were found. Immunofluorescence showed generalized and diffuse subendothelial deposits of IgM, C3 and κ-type light chains (Figure 1). Stains for IgG, IgA and λ-chains were negative. No glomeruli were contained in the sample for electronic microscopy. Because of the presence of active glomerular disease apparently related to monoclonal protein deposition,
treatment with prednisone at an initial dose of 30 mg/day and chlorambucil at 5 mg/day was started. After 1-year of therapy, monoclonal and k chains in serum and urine immunofixation had disappeared. Serum IgM levels remained high. Proteinuria was unchanged and renal function worsened, reaching end-stage renal failure 2 years after his first admission to our hospital.

After 5 years, the patient was asymptomatic in a well-tolerated haemodialysis programme. Serum level of IgM remained high: 406 mg/dl. The IgA level dropped to 51 mg/dl and the IgG level was normal at 790 mg/dl. Serum immunofixation ruled out monoclonal proteins. A new bone marrow biopsy showed no atypical lymphocyte infiltration, and thoracic and abdominal CT showed no adenopathies or visceral enlargement. After these negative results, the patient was placed on the waiting list for renal transplantation.

Discussion

Renal involvement is a frequent finding in monoclonal gammopathies. Histological and ultrastructural features distinguish three forms of monoclonal immunoglobin deposition disease. The commonest is light-chain amyloid disease, which is characterized by Congo red binding deposits, with green birefringence under polarization microscopy. At ultrastructure, organized deposits with a fibrillar ultra structure are seen. The second form includes cryoglobulinaemic kidney and immunotactoid glomerulonephritis that have distinguishable light and fluorescence pictures sharing organized microtubule formation at electron microscopy. In a third category, light, heavy or light and heavy-chain deposition disease of a single immunoglobulin class, with non-organized disposition at ultrastructure is developed and defines the disease now called monoclonal immunoglobin deposition disease (MIDD) [9]. To differentiate these subsets, renal biopsy is needed [10].

Although we could not obtain tissue for ultrastructural study, we believe that light and immunofluorescence microscopy allowed us to classify this case as MIDD according to the algorithm proposed by Korbet [11]. Moreover, we consider that amyloidosis was an improbable diagnosis due to the negativity of Red Congo. In the same way, we discarded the cryoglobulinaemic glomerulonephritis because of the absence of cryoglobulinaemia, rheumatoid factor or hypocomplementaemia. Immunotactoid glomerulonephritis can also be excluded because in this entity, when paraprotein deposits are described, these are constituted by IgG in more than 90% of the cases [12,13]. Based on these immunopathological criteria, we have classified this case as a MIDD.

MIDD is observed mainly in the setting of malignancy. Interestingly, ‘idiopathic’ renal MIDD has also been observed in monoclonal gammopathies, but without satisfying criteria for a diagnosis of malignant disease, namely bone marrow pathology or visceral or bone lesions. Among patients with idiopathic renal MIDD, IgG or IgA gammopathies have been described [3,14], but MIDD in the setting of non-malignant IgM monoclonal gammopathy has rarely been described [7,8].

Monoclonal IgM gammopathy can be found as part of Waldenström’s disease, in association with malignant forms of lymphoma and rarely associated with infectious or inflammatory conditions. In some instances it is a relatively stable abnormality, in the absence of other identifiable disease [15].

Recently, consensus panel recommendations from the second international workshop on Waldenström’s macroglobulinaemia proposed four categories for IgM monoclonal gammopathies: Waldenström’s disease for patients with bone marrow infiltration by lymphoplasmacytic lymphoma who might or might not have symptoms attributable to IgM (symptomatic or asymptomatic Waldenström’s disease: first and second categories, respectively). Thirdly, the term ‘IgM–related disorders’ is proposed for patients without bone marrow infiltration, but who present symptoms attributable to IgM, mainly those of an autoimmune nature like peripheral neuropathy or cold agglutinin disease. Fourth, monoclonal gammopathy of unknown significance (MGUS) is the label for those patients with IgM monoclonal gammopathy with no bone marrow infiltration and no IgM-related symptoms [16].

The most frequently described form of renal involvement in Waldenström’s disease is the direct infiltration of the kidney by atypical lymphoid cells, which occurs in 50–60% of patients [2,17,18]. Less frequently described (7–31%) glomerular involvement is found typically in mesangial proliferative or mesangio-capillary glomerulonephritis with IgM deposits in the mesangium and/or along the glomerular basement membrane. Cryoglobulinaemic or amyloidotic features can be found as well [19].

In line with previous classification, the reported case could be diagnosed as an ‘IgM-related disorder’. Fig. 1. Immunofluorescence showed diffuse subendothelial deposits of IgM, C3 and k-type light-chains.
in which symptoms attributable to monoclonal IgM are renal nephrotic syndromes with microscopic haematuria and progressive renal failure. Renal biopsy showed a mesangiocapillary pattern of glomerulonephritis with IgM and κ light-chain deposits. These clinical–pathological features are identical to those observed in some patients with Waldenström’s disease, but in this case in the setting of a non-malignant monoclonal IgM gammopathy. Thus, the patient showed normal bone marrow biopsy at the moment of diagnosis with no visceral or other clinical involvement related to paraprotein.

Treatment recommendations for Waldenström’s macroglobulinaemia were established in the aforementioned workshop and vary according to the different statements of disease [20]. Therapy should not be based on IgM levels, but this may be reasonable for those patients who demonstrate rising IgM levels with progressive signs or symptoms of disease. There are several choices for first-line therapy, such as alkalisng agents, nucleoside analogues and rituximab. Other alternate first-line treatment consists of autologous stem cell transplantation, allogenic transplantation, plasmapheresis and corticosteroids or splenectomy.

If renal involvement is of amyloid or light-chain deposition disease, patients are generally treated with chemotherapy and supportive care, to minimize the risk factors that promote light-chain filtration and subsequent obstruction by cast formation within the tubules [21].

Outcome of renal involvement in monoclonal gammopathies is variable according to the series. The proportion of patients with severe renal failure at presentation of disease is reported from 1.8% to 30% [3,22,23]. Pozzi and colleagues [24] reported that 36% of the patients developed end-stage renal disease (ESRD), despite treatment in the first month; and Lin and colleagues [3] observed that none of the patients who presented with ESRD or required dialysis improved at the end of follow-up. Interestingly, Heilman and colleagues [25] reported that 62% of the patients with renal light chain deposition disease improved or stabilized their renal function if chemotherapy was started when serum creatinine was <354 μmol/l (4 mg/dl). In our case, therapy with prednisone and chlorambucil was initiated when serum creatinine was 252 μmol/l and it lasted for 1 year. Despite the fact that paraprotein was no longer present in serum and urine, renal failure progressed to ESRD. After 5 years of haemodialysis treatment, the patient remained well in a clinical condition, no paraprotein was detected in serum, and a new bone marrow biopsy and CT exploration ruled out abnormalities suggesting lymphoplasmacytic lymphoma. As haematological disturbance did not progress to malignant disease, no strict contraindication for renal transplantation was found, according to Dagher et al. [26] and Rostaing et al. [27]. Thus, after the appropriate information to the patient, we decided to place him on the waiting list for renal transplantation, despite the theoretical possibility of the recurrence of paraprotein deposits in the renal graft [28,29].

The most interesting suggestion derived from this clinical observation is that renal involvement should be searched for in patients with IgM monoclonal gammopathy, even though this is benign. Appearance of abnormalities in renal routine tests deserves more in-depth diagnostic procedures, including renal biopsy. In case of paraprotein deposits, subsequent therapeutic measures must be taken, in view of the possible evolution to progressive renal failure.

Conflict of interest statement. None declared.

References


Received for publication: 12.9.06
Accepted in revised form: 31.10.06