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Clinical Report

Discrete renal deposition of IgM heavy chain and κ light chain in Waldenström macroglobulinemia (IgM-κ)

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Abstract

We report previously undescribed renal lesions associated with monoclonal gammopathy in a 59-year-old man with Waldenström macroglobulinemia (IgM-κ). Light microscopy showed mesangial proliferation and thickening of glomerular basement membranes (GBMs) and tubular basement membranes (TBMs). Neither intraglomerular thrombi nor nodular glomerulosclerosis was observed. Immunofluorescence studies disclosed essentially discrete localization of IgM heavy chain within the mesangial area and κ light chain along GBMs and TBMs. Electron microscopy showed continuous linear deposits of finely granular electron-dense material along the inner aspect of GBMs and TBMs. Repeated rituximab treatment and chemotherapy (melphalan and prednisolone) led to the improvement of proteinuria.

Keywords: kidney lesion; monoclonal immunoglobulin deposition disease; rituximab; Waldenström macroglobulinemia

Introduction

Kidney diseases associated with monoclonal gammopathies are divided into two subgroups [1]. The first group is characterized by organized deposits, like fibrils (mainly in amyloidosis) or microtubules (cryoglobulinemia). The second group represents granular electron-dense deposits and defines entities named Randall type monoclonal immunoglobulin deposition disease (MIDD) [2]. MIDD is characterized by the presence of nodular glomerulosclerosis by light microscopy, monoclonal linear staining along the glomerular basement membranes (GBMs) and tubular basement membranes (TBMs) by immunofluorescence and continuous linear deposits of fine granular electron-dense material along the inner aspect of GBMs and TBMs by electron microscopy [2, 3]. Three subtypes of MIDD have been reported, including light chain deposition disease (LCDD), light and heavy chain deposition disease (LHCDD) and heavy chain deposition disease [3].

Waldenström macroglobulinemia (WM) is a clonal B-cell lymphoproliferative disorder characterized by bone marrow infiltration associated with IgM monoclonal gammopathy [4]. Although renal complications of WM are rare, a wide spectrum of lesions, such as amyloidosis, cryoglobulinemia-related glomerulonephritis, intracapillary monoclonal deposit disease and cast nephropathy, has been observed [5]. Here, we report previously undescribed renal lesions in a patient with WM.

Case report

A 59-year-old man with a 1-year history of diabetes mellitus developed edema in September 2008. Proteinuria and an increased level of serum IgM were found in another hospital and he was referred to our hospital for further examination 2 months later. On admission, blood pressure was 130/96 mmHg. A physical examination showed bilateral pretibial edema.

The total urinary protein level for 24 h was 0.85 g, and urine sediments showed no hematuria. Urinary β2-microglobulin was >80 000 μg/L (normal <250 μg/L). Hemoglobin was 152 g/L, white-cell count 7.8×10^9/L and platelet count 288×10^9/L. Serum total protein was 78 g/L, albumin 44 g/L, blood urea nitrogen 4.14 mmol/L, creatinine 90.2 μmol/L, aspartate aminotransferase 38 IU/L, alanine aminotransferase 43 IU/L, lactate dehydrogenase 198 IU/L and hemoglobin A1c 6.0%. Serum IgG was 11.30 g/L, IgA 3.21 g/L, IgM 10.20 g/L, C3 0.34 g/L, C4 0.17 g/L, CH50 33 U/mL and C-reactive protein 2.06 mg/dL. Serum and urinary protein electrophoresis showed IgM-κ monoclonal protein and Bence-Jones κ protein. Serum anti-nuclear antibodies and cryoglobulins were negative, and circulating immune complexes were not detected. A chest X-ray film showed no abnormalities. An electrocardiogram revealed left ventricular hypertrophy. A systemic gallium scan was normal. A systemic enhanced computed tomography scan showed no lymphadenopathy or hepatosplenomegaly.

A bone marrow examination showed increased small lymphocytes showing plasmacytoid differentiation (14%). Flow cytometry showed IgM^+, κ^+, $CD5^-$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$ and $CD25^+$ B-cell populations. The chromosomal karyotype was 46 XY. Polymerase chain reaction analysis showed the rearrangement of the immunoglobulin heavy chain and κ light chain genes.

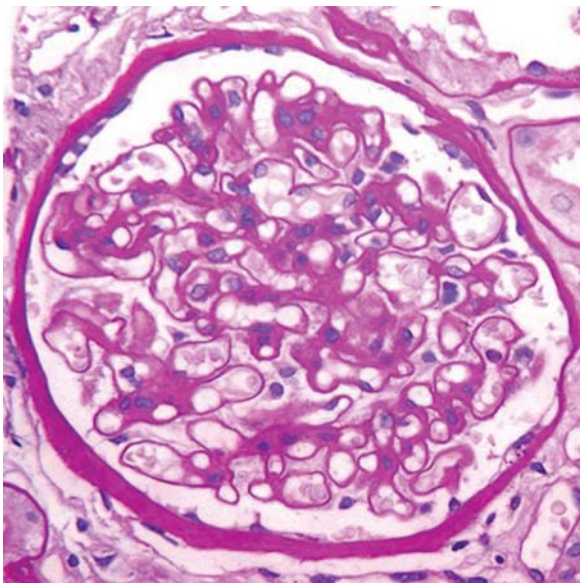

Fig. 1. Light microscopy shows the mild mesangial proliferation and thickening of the glomerular capillary walls, Bowman's capsule and TBMs. Periodic acid-Schiff staining (×400).

Kidney biopsy showed a diffuse mild mesangial proliferation and thickening of the glomerular capillary walls, Bowman's capsule and TBMs (Figure 1). Neither intraglomerular deposits nor nodular glomerulosclerosis were observed. There were focal interstitial infiltration of lymphocytes and mild arteriolar hyalinosis. Tubular casts with macrophagic reactions were not seen. Congo red staining for amyloid was negative. Immunofluorescence studies showed strong granular staining for IgM within the mesangial area (Figure 2A) and strong linear staining for κ light chain mainly along GBMs and TBMs (Figure 2B). The intensity of λ light chain was faint (Figure 2C). Weak granular staining for IgA, C3 and C1q was noted within the mesangial area. Dual immunostaining disclosed essentially discrete glomerular localization IgM heavy chain and κ light chain (Figure 3A–C). On electron microscopy, continuous linear deposits of finely granular electron-dense material were observed along the inner aspects of GBMs (Figure 4A) and TBMs (Figure 4B). Granular electron-dense deposits mimicking immune complex-type deposits were also observed in the mesangial area. There were no organized structures.

From these findings, the patient was diagnosed with monoclonal IgM-κ deposition disease associated with WM. He was treated with 650 mg of rituximab (anti-CD20 monoclonal antibody) and was discharged in December. In the outpatient clinic, he was treated with an additional four courses of rituximab therapy. From May 2009 to April

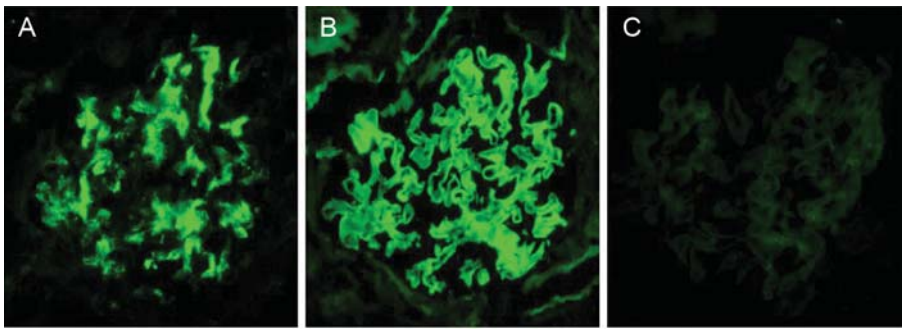

Fig. 2. Immunofluorescence microscopy for IgM heavy chain (**A**), κ light chain (**B**) and λ light chain (**C**) displays strong granular staining for IgM heavy chain within the mesangial area and linear staining for κ light chain along glomerular capillary walls and TBMs, but no significant staining for λ light chain (×400).

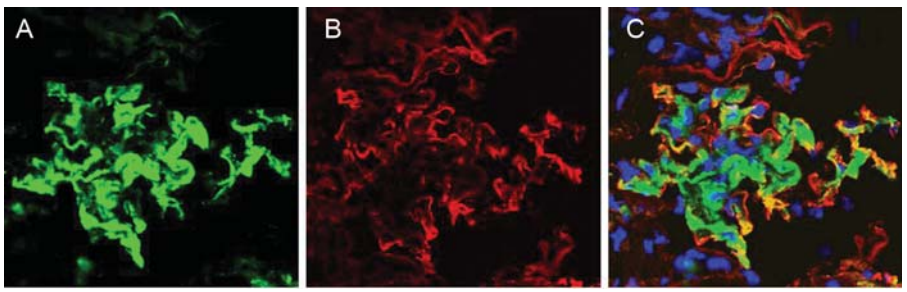

Fig. 3. Dual immunostaining by antibodies to IgM heavy chain and κ light chain. A kidney specimen was stained with fluorescein isothiocyanate-conjugated rabbit antibody to human IgM (μ heavy chain) (DakoCytomation, Glostrup, Denmark), mouse antibody to human κ light chain (Abcam, Tokyo, Japan) and Alexa Fluor 546 anti-mouse IgG (Molecular Probes, Eugene, OR, USA) and Vectashield Mounting Medium with 4′, 6-diamidino-2-phenylindole (DAPI; Vector Laboratories, Burlingame, CA, USA). (**A**) Granular lumpy deposits of IgM heavy chain mainly in the mesangial area are shown in green. (**B**) Linear deposits of κ light chain mainly along the glomerular capillary walls are shown in red. (**C**) The merge image shows almost completely discrete localization of IgM heavy chain and κ light chain. Nuclei are shown in blue.

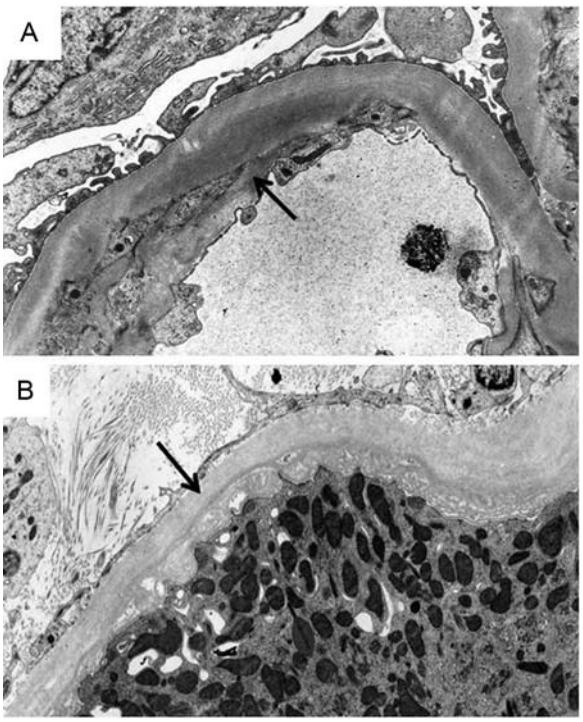

Fig. 4. Electron microscopy reveals continuous linear deposits of finely granular electron-dense material along the inner aspect of the GBM (**A**) and TBM (**B**).

2011, he was treated with eight courses of MP chemotherapy (melphalan 8 mg/day for 4 days and prednisolone 60 mg/day for 4 days). At a follow-up in March 2012, he was well. At that time, urinary protein was 0.11 g/g creatinine, urinary β2-microglobulin 203 μg/L, serum creatinine 111.4 μmoL/L and serum IgM 3.89 g/L.

Discussion

In our patient with IgM monoclonal gammopathy, diagnosis of WM was made based on an immunophenotypic profile of bone marrow infiltration cells (a surface IgM-positive $CD5^{-}CD10^{-}CD19^{+}CD20^{+}CD23^{-}$ immunophenotype) [4]. Our patient developed a unique combination of renal lesions associated with IgM monoclonal gammopathy. Repeated rituximab treatment and MP chemotherapy led to the improvement of his proteinuria.

Since the first description of renal pathology in 16 cases of WM in 1970 [6], there have been few reports on WM-related nephropathies. According to a study of 7 patients with WM by Audard *et al*. [5] and their review of the literature, WM-related nephropathies include characteristic intracapillary deposits of IgM, amyloidosis, cryoglobulinemia-related glomerulonephritis, immunotactoid/fibrillary glomerulopathy, membranoproliferative glomerulonephritis without cryoglobulinemia, crescentic glomerulonephritis, cast nephropathy and Fanconi syndrome. Few cases of nodular nonamyloidotic glomerulopathy (probable MIDD) [7, 8] or MIDD [9] have been described in the literature. However, these cases were not characterized, or not well characterized, by immunofluorescence studies.

In our patient with circulating monoclonal IgM-κ, pathological findings were the mild mesangial proliferation and thickening of GBMs and TBMs, without intraglomerular deposits or nodular formation. In the glomeruli, there was discrete deposition of IgM heavy chain within the mesangial area and κ light chain along GBMs. Deposition of κ light chain along TBMs was also observed. This deposition pattern is different from that of LHCDD, in which glomerular colocalization of monoclonal light and heavy chains can be observed [10]. We speculate that IgM heavy chain and κ light chain precipitated separately, as an independent rather than as a whole immunoglobulin molecule, and that mesangial IgM heavy chain deposits contributed little to proteinuria and renal insufficiency in our patient. Immunohistochemical and ultrastructural findings of deposits along the GBMs and TBMs were consistent with those in κ-LCDD [2, 3] as a result of free light chain nephrotoxicity [11]. A similar case of κ-LCDD in a patient with circulating IgM-κ was reported by Nakamoto *et al*. [12]: typical pathological findings of nodular glomerulosclerosis with a selective κ light chain deposition and without IgM heavy chain deposition were observed. In contrast with this case, only mild mesangial expansion was seen in our case. Therefore, not all light chain deposits on GBMs are able to induce nodular glomerulosclerosis in LCDD, as pointed out by Touchard *et al*. [13]. Although pathogenesis of extracellular matrix accumulation in LCDD is not well known, roles of signaling pathways that are triggered by light chain binding to mesangial cells are suggested [11].

The main choices for the primary treatment of WM are alkylating agents including melphalan and rituximab [4]. Plasma exchange is indicated for the acute management of patients with symptoms of hyperviscosity [4]. In our patient, rituximab treatment followed by MP chemotherapy resulted in the amelioration of proteinuria and the prevention of progressive renal dysfunction.

In summary, we consider that previously unreported renal lesions in our WM patient fall within the wide spectrum of kidney lesions associated with IgM-secreting monoclonal proliferations [5]. Accumulation of further cases is needed to clarify clinicopathological features and prognosis of this unique WM-associated renal disease.

Conflict of interest statement. None declared.

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