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 (LHCDDD) and heavy chain deposition disease (HCDDD) 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 × 10⁹/L and platelet count 288 × 10⁹/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.

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
In our patient with circulating monoclonal IgM-κ, pathological findings were the mild mesangial proliferation and thickening of GBMs and TBM s, 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 TBM s 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 deposition contributed little to proteinuria and renal insufficiency in our patient. Immunohistochemical and ultrastructural findings of deposits along the GBMs and TBM s 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.

**References**

1. Santostefano M, Zanchelli F, Zaccaria A et al. The ultrastructural basis of renal pathology in monoclonal gammopathies. J Nephrol 2005; 18: 659–675
2. Preud’homme J-L, Aucouturier P, Touchard G et al. Monoclonal immunoglobulin deposition disease (Randall type). Relationship with structural abnormalities of immunoglobulin chains. Kidney Int 1994; 46: 965–972
3. Lin J, Markowitz GS, Valeri AM et al. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. J Am Soc Nephrol 2001; 12: 1482–1492
4. Vijay A, Gertz MA. Waldenström macroglobulinemia. Blood 2007; 109: 5096–5103
5. Audard V, Georges B, Vanhille P et al. Renal lesions associated with IgM-secreting monoclonal proliferations: revisiting the disease spectrum. Clin J Am Soc Nephrol 2008; 3: 1339–1349
6. Morel-Maroger L, Basch A, Donan F et al. Pathology of the kidney in Waldenström’s macroglobulinemia. Study of sixteen cases. N Engl J Med 1970; 283: 123–129
7. Lin JH, Orofino D, Sherlock J et al. Waldenström’s macroglobulinemia, mesangio-capillary glomerulonephritis, angiitis and myositis. Nephron 1973; 10: 262–270
8. Zlotnick A, Rosenmann E. Renal pathologic findings associated with monoclonal gammopathies. Arch Intern Med 1975; 135: 40–45
9. Martelo OJ, Schultz DR, Pardo V, Perez-Stable E. Immunologically-mediated renal disease in Waldenström’s macroglobulinemia. Am J Med 1975; 58: 567–575
10. Masai R, Wakui H, Togashi M et al. Clinicopathological features and prognosis in immunoglobulin light and heavy chain deposition disease. Clin Nephrol 2009; 71: 9–20
11. Ronco P, Plaisier E, Mougenot B, Aucouturier P. Immunoglobulin light (heavy)-chain deposition disease: from molecular medicine to pathophysiology-driven therapy. Clin J Am Soc Nephrol 2006; 1: 1342–1350
12. Nakamoto Y, Imai H, Hamanaka S et al. IgM monoclonal gammopathy accompanied by nodular glomerulosclerosis, urine-concentrating defect, and hyporeninemic hypoaldosteronism. Am J Nephrol 1985; 5: 53–58
13. Touchard G. Ultrastructural pattern and classification of renal monoclonal immunoglobulin deposits. In: Touchard G, Aucouturier P, Hermine O, Ronco P (eds). Monoclonal Gammapathies and the Kidney. Dordrecht, Boston, London: Kluwer Academic Publishers, 2003, pp. 95–117

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