

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: A Poorly-Understood Disease Spectrum

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Description

Nonamyloidotic monoclonal immunoglobulin (Ig) deposition disease (MIDD) includes heavy-chain deposition disease (HCDD), light- and heavy-chain deposition disease (LHCDD), and light-chain deposition disease (LCDD); all of these are associated with free light- or heavy-chain deposition [1]. These diseases typically show nodular glomerulosclerosis resembling diabetic nodular glomerulosclerosis and continuous linear deposition of fine granular electron-dense materials along the inner aspect of glomerular basement membranes, in the mesangium, and on tubular basement membranes. Another nonamyloidotic disease with monoclonal Ig deposits is proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID), which is a rare but remarkable entity characterized by glomerular deposits of IgG, containing an intact (whole) Ig composed of a single light-chain isotype and a single γ heavy-chain subclass [2]. Recently, this disease has been recognized to morphologically show membranoproliferative glomerulonephritis (MPGN)-like lesions and granular deposits mimicking immune-complex-type deposits in subendothelial areas and the mesangium, and absent on tubular basement membranes. In other words, three differences between MIDD and PGNMID are recognized as follows: 1) light microscopic findings, which are similar to either nodular diabetic glomerulosclerosis or MPGN; 2) the distributions of electron-dense deposits, which are either fine granular electron-dense materials along the inner aspect of glomerular basement membranes, in the mesangium, and on tubular basement membranes, or immune-complex-type deposits in the subendothelial and mesangial areas; and 3) the natures of monoclonal materials, which are free light- or heavy-chains or intact (whole) Igs. The term "PGNMID" is obviously used to indicate proliferative glomerulonephritis with monoclonal IgG deposits. However, whether the pathological condition of "proliferative glomerulonephritis (PGN) with monoclonal Ig deposits" arises only from IgG abnormalities is unanswered. Although rare, cases of PGN similar to MPGN associated with monoclonal IgA or IgM deposits have been reported recently [3-14]. These cases show deposits of an IgA or IgM one class heavy-chain together with those of a κ or λ one class light-chain in the subendothelial and mesangial areas without tubular basement membrane deposits. Based solely on the deposition pattern of heavy- and light-chains in these cases, LHCDD of MIDD cannot be excluded. However, when the above mentioned differences between LHCDD and PGNMID are adapted to such cases, the light microscopic findings and distributions of deposits using immunofluorescence (IF) and electron microscopy are entirely different in PGN with monoclonal IgA or IgM deposits compared with those in LHCDD.

To the best of our knowledge, there have been 11 reported cases that could be considered to be PGN with monoclonal IgA deposits [3-7]. Recently, we experienced an additional case. A 59-year old man was presented for rapidly progressive glomerulonephritis with nephrotic syndrome. His serum electrophoresis showed the presence

of monoclonal IgA- λ , but the serum free κ/λ ratio was normal. Renal biopsy (Figure 1) showed diffuse MPGN-like lesions with IgA1 heavy-chain and λ light-chain deposits, both of which were observed in a similar distribution. On electron microscopy, fine granular electron-dense deposits were found in subendothelial areas, mimicking immune complex-type deposits. No underlying lymphoplasmacytic disorders were identified. The patient reached complete remission with corticosteroid treatment including steroid pulse therapy. In the 12 cases including our additional case, the predominant IF pattern was IgA- κ (n=9), followed by IgA- λ (n=3). Only 2 cases had multiple myeloma as underlying disorders. Prognosis was described in 5 cases: complete remission in 2, end stage kidney disease in 2 and no response in 1. It is possible that PGN with monoclonal IgA deposits may be overlooked, because IgA nephropathy is the most common primary glomerular disease and, actually, light-chain staining is not performed routinely at most institutes. MPGN with IgA-dominant deposits requires a careful examination including light-chain and IgA subclass staining.

Cases considered as PGN with monoclonal IgM deposits have also been reported with approximately the same frequency as those with monoclonal IgA deposits, and we found 16 cases in the literature [8-14]. All cases except one showed monoclonal IgM- κ deposits, and the 9 cases in which the sex was noted were males. Seven cases had hematological diseases such as Waldenström's macroglobulinemia (WM), B-cell lymphoma, and chronic lymphocytic leukemia (CLL); however, 8 cases had no apparent hematological disorders. Prognosis was described in 8 cases: complete remission in 1 with WM, partial remission in 2 with no hematological disorders and 1 with CLL, end-stage kidney disease in 2 with WM and 1 with no hematological disorders, and no response in 1 with WM.

IgG heavy-chains and κ or λ light-chains that deposit in glomeruli of PGNMID cases exists in the form of intact (whole) Ig [2]. In contrast, two different observations of dual immunostaining have been reported in LHCDD cases: 1) light- and heavy-chains precipitated separately, as independent rather than as intact (whole) Ig molecules [15]; and 2) paraprotein deposits were intact (whole) Ig molecules [16]. However, a common observation in these cases was free light-chain deposits mainly observed on tubular basement membranes. In cases considered as PGN with monoclonal IgA and IgM deposits, the serum free κ/λ ratio was examined in three cases including our additional one case, and it was

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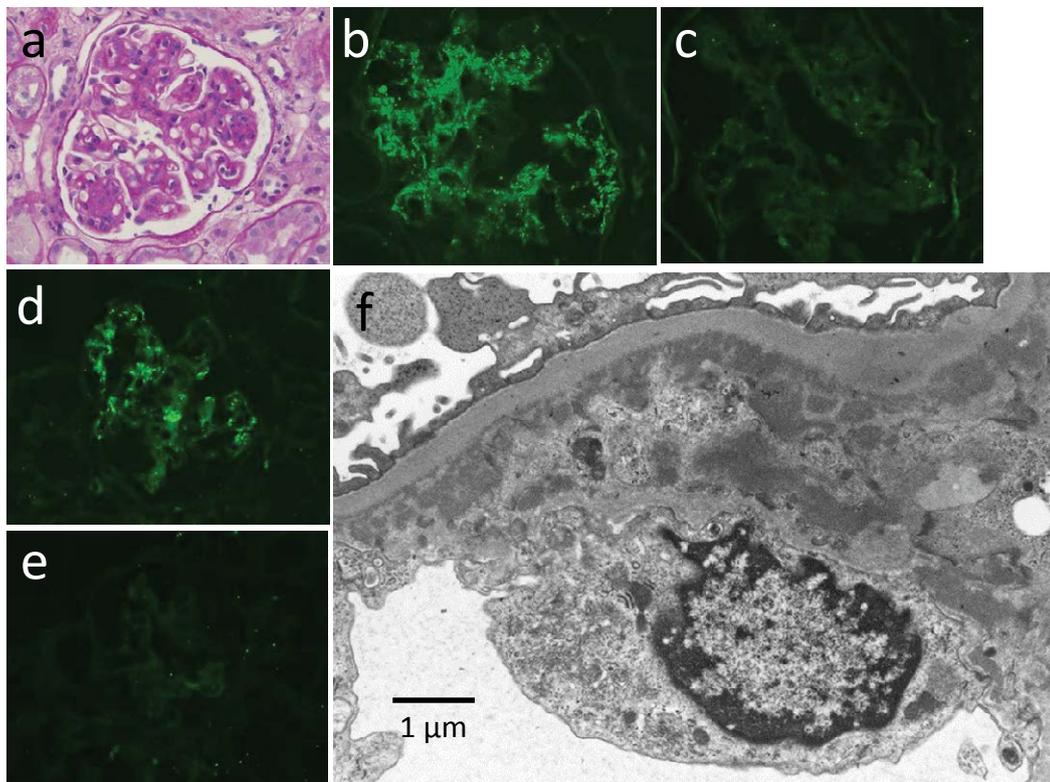


Figure 1: Renal biopsy findings from a 59-year old man. Membranoproliferative-like glomerular change was observed (a) associated with IgA1 heavy-chain deposits but without IgA2 heavy-chain deposits (b and c). Light-chain staining was positive only for λ light-chains (d and e). Electron-dense deposits, mimicking immune-complex types, were observed in the subendothelium and mesangium (f). (a), PAS stain $\times 200$; (b and c), $\times 300$; and (d and e), $\times 200$.

entirely normal in all of them [6,13]. This is an important finding that indirectly demonstrates that circulating and deposited monoclonal IgA and IgM are intact (whole) Igs.

In summary, PGNMID is a well-known and distinct disease entity; however, the disease concept of PGN with monoclonal IgA or IgM deposits has not been adequately established or understood, although the etiology of the latter is nearly identical to that of the former. PGN with monoclonal Ig deposits should be categorized into PGN with monoclonal IgG, IgA, or IgM deposits, which more accurately describes the essential features.

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