Abstract:
A 63-year-old man with an 8-year history of proteinuria was diagnosed with nephrotic syndrome, and a renal biopsy was performed. Light and electron microscopic analyses showed classic features of idiopathic membranous nephropathy (IMN). However, immunofluorescence tests revealed solitary polyclonal granular IgA deposition along the glomerular capillary walls, rather than IgG, which is often dominant in IMN. The combined use of corticosteroids and calcineurin inhibitor was noticeably effective in reducing proteinuria and improving edema in the current case. Two additional rare cases of IMN with solitary IgA deposition were reviewed, and long-term surveillance is still warranted to characterize its clinicopathological features and outcome.

Key words: membranous nephropathy, solitary polyclonal IgA deposition, rare disease, case report

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by IgA and/or C1q (6).

Each subclass of IG has unique biological activities, and these subclasses may be preferentially produced in response to different antigens. However, the involvement of different IG subclasses in the pathogenesis of MN is still not fully elucidated. To our knowledge, only two unusual IMN cases with solitary polyclonal IgA deposition have been reported by Japanese authors (2015 and 2019) (7, 8). Findings from these two cases are consistent with regard to the main features of granular deposition of solitary polyclonal IgA on immunofluorescence and quick remission upon the administration of immunosuppressive induction therapy. We herein report an additional case of IMN with solitary IgA deposition and clarify the characteristics of this unique entity through a literature review.

Case Report

A 60-year-old man with an 8-year history of proteinuria (1+ to 3+) and hematuria (1+ to 3+) was referred to our hospital due to generalized edema of the lower extremities and foamy urine. One year ago, he had been diagnosed with acute myocardial infarction and underwent coronary stent implantation; thereafter, he was treated with aspirin and clopidogrel. On admission, a physical examination showed pitting edema in his lower extremities; however, no abnormal signs were observed in the lungs, heart or abdomen. A urinalysis revealed proteinuria (3+; 3.76 g/day) and hematuria (2+; red blood cell count: 15/high-power field). Laboratory studies revealed a hemoglobin level of 13.9 g/dL, and serum chemistry showed a blood urea nitrogen level of 38.4 mg/dL and serum creatinine level of 0.62 mg/dL, low total serum protein level of 62 mg/dL, total cholesterol level of 162.79 mg/dL, and albumin level of 2 g/dL. During the first admission, given the low-grade proteinuria (<4 g/day) and normal renal function in the present case, neither corticosteroid nor immunosuppressive therapy was started aside from supportive care, which consisted of the use of an angiotensin II receptor blocker (valsartan), lipid-lowering agents (atorvastatin and ezetimibe) and anti-platelet drug (clopidogrel). However, no remission was observed 4 months later at the second admission, and the 24-h urine protein continuously increased to 4.76 g, while serum albumin decreased to 1.8 g/dL, accompanied by worsened swelling of the extremities, eyelid edema and oliguria. The combined use of steroid and calcineurin inhibitor (prednisolone 30 mg daily for 8 weeks, tacrolimus 3 mg every 12 h for 1 week with a target blood concentration of 3-5 ng/mL and then gradually tapered) was administrated (9).

After two months of treatment, the present case was completely resolved, as evidenced by the disappearance of proteinuria and hematuria on a urinalysis. The proteinuria declined to <0.15 g/day, and the serum albumin normalized to 3.9 g/dL without symptoms of edema. The patient has been closely followed thus far, but exhaustive screening tests to determine the underlying cause of SMN has yet to yield any clues.

Discussion

We encountered a pathologically diagnosed IMN patient with typical membranous features on light and electron microscopic examinations of renal biopsy tissue. Of note, granular deposition of solitary IgA, but not IgG, IgM or C3, was observed along the glomerular capillary walls on immunofluo-
rescence; however, no underlying secondary diseases were found during the follow-up period. Therefore, the clinical and pathological findings, except for those of immunofluorescence, were all compatible with a diagnosis of IMN. To our knowledge, this is the third reported case of IMN with solitary IgA deposition.

Mounting evidence indicates that the distinction between IMN and SMN can be suggested by IgG subclasses. An already-known fact is that most renal biopsies with IMN are characterized by IgG4-dominant glomerular deposits (10). In contrast, the presence of IgG1, IgG2, IgG3, IgM, IgA, and C1q is closely related to SMN (5, 10). In particular, secondary causes should be suspected when IgG deposits are accompanied by IgA deposits (4). Therefore, in our current case, although the depositions of IgG and all IgG subclasses were deficient, the markedly elevated IgA depositions were highly suggestive of SMN at the outset, and various attempts were made to determine the cause of the putative SMN; however, despite two years of such efforts, the results of all examinations excluded the possible existence of autoimmune disease, infection and malignancy. For example, LN, the most common visceral manifestation of systemic lupus erythematous (SLE) and the most important secondary form of MN, was first suspected in our case due to his per-
Electron microscopy image showing granular electron-dense deposits and extensive foot process effacement of the podocyte (original magnification ×5,000).

Of note, only two cases of IMN with solitary polyclonal IgA deposition have been described previously, namely by Kobayashi et al. (7) in 2015 and by Sawamura et al. (8) in 2019. Table summarizes the clinicopathological findings in the previously reported cases and our present case. These three Asian patients developed NS with a preserved renal function. Anti-nuclear antibodies, cryoglobulin and monoclonal proteins were not detected. Consistent membranous features accompanied by solitary IgA immune deposits were displayed in the current three cases, and positive κ- and λ-light chains along the glomerular capillary walls further confirmed the polyclonal origin of the IgA immune deposits. With respect to the consistent immune features in three cases, the deficiency of PLA2R and C3 may have profound implications. Previous evidence documented that a positive staining with PLA2R on a renal biopsy was able to identify IMN with 97% specificity (11), and most patients diagnosed with IMN have IgG4-dominant subepithelial immune complex deposits that colocalize with the PLA2R to podocytes. The deficiency of PLA2R in these three cases thus suggests that other known autoantigens or exogenous mucosal antigens, such as bacterial antigens, may be associated with solitary polyclonal IgA deposition. Furthermore, C3 deposits are another hallmark seen in more than half of IMN patients (6), so we speculate that the shortage in complement deposition may be related to the special mechanism underlying the onset of solitary IgA deposition, and complement activation may be dispensable during this process.

Notably, low- or medium-dose prednisone therapy was effective for treating NS in the two previously reported cases, while the combined use of medium-dose prednisone and tacrolimus induced remission in our present case. In brief, the quick response to induction therapy suggests a high incidence of remission in this pathological subtype, and the lack of any record of relapse over a long follow-up strengthens our belief in a good prognosis for this unique subtype, despite the fact that the predictable correlation between this pathological subtype with remission rate and recurrence rate remains undetermined. All things considered, we believe these three rare cases call into question the established theories and may help clarify the mechanistic variety involved in the development of MN.

Although the physiological and cellular mechanisms underlying the solitary IgA deposition in MN remains elusive, there are several variants of glomerular disease with IgA deposits combined with capillary wall abnormalities. The first entity that should be considered in the differential diagnosis is concomitant IgA nephropathy (IgAN) and MN (referred to as combined IgAN-MN). According to the study of the largest patient cohort diagnosed with combined IgAN-MN (n=73), all patients had mesangial IgA-dominant deposits accompanied by obviously increased mesangial cell proliferation (12). IgAN is characterized by mesangial deposition of IgA, hence this feature is considered as the most evident point to distinguish combined IgAN-MN from MN, and this highly specific histological attribute of IgAN was not noted in the two previously reported cases or our present case. Furthermore, the presence of capillary wall IgG immune deposits was observed in all cases with combined IgAN-MN (12, 13), although these findings were not observed on immunofluorescence in our current case or the two previous cases. Taken together, the characteristic immunofluorescence findings and pathological features of combined IgAN-MN can ensure the early identification of this entity and help avoid missing a diagnosis of a rare case of MN with solitary IgA deposition.

In addition, given the essential role of IgA in protecting against infections on mucosal surfaces, such as those exposed to tears, saliva, colostrum, genital, respiratory or gas-
trointestinal secretions, a hypothesis concerning postinfectious glomerular nephritis (PIGN) was proposed. Most cases of PIGN are triggered by nephritogenic strains of group A beta-hemolytic streptococcus, with less common pathogens being nonstreptococcal bacteria, viruses, parasites, rickettsiae and fungi. The clinical presentation of PIGN varies

| Table. Summary of Three Rare Cases of MN with Solitary IgA Deposition. | Reported case 1 [7] | Reported case 2 [8] | Present case |
|---|---|---|---|
| Age (years) | 71 | 60 | 60 |
| Gender | Female | Male | Male |
| Hypertension | (+) | (-) | (-) |
| Edema | (+) | (+) | (+) |
| Complication | None | T2DM | CHD |
| Proteinuria (g/day or g/g creatinine) | 4.8 | 5.1 | 4.8 |
| Microscopic hematuria (>5 RBC/HPF) | (+) | (-) | (+) |
| Serum albumin (g/dL) | 2.1 | 2.4 | 1.8 |
| Serum creatinine (mg/dL) | 0.8 | 0.79 | 0.62 |
| White blood cell (µL) | ND | 5,900 | 5,560 |
| Serum C3 (mg/dL) | 147 | 80 | 127 |
| Serum C4 (mg/dL) | 32 | 12 | 16 |
| Hepatitis B virus antigen | (-) | (-) | (-) |
| Serum antinuclear antibody | (-) | (-) | (-) |
| Serum cryoglobulin | ND | (-) | (-) |
| Serum IgG (mg/dL) | 1,030 | 572 | 728 |
| Serum IgA (mg/dL) | 271 | 345 | 272 |
| Serum IgM (mg/dL) | ND | 93 | 128 |
| Monoclonal protein | Serum (-) | (-) | (-) |
| Urine (-) | (-) | (-) | (-) |
| Treatment (initial dose) | PSL (25 mg/day) | PSL (10 mg/day) | PSL (30 mg/day) + TAC (2 mg q12h) |
| Follow-up period (year) | 8 | 3 | 1 |
| Proteinuria (g/day or g/g creatinine) at follow-up | 2 | 2.1 | <0.15 |
| Serum creatinine (mg/dL) at follow-up | ND | 0.87 | 0.79 |
| Light microscopy | Number(s) of glomeruli | 12 | 20 | 11 |
| Number(s) of sclerosis | 1 | 2 | 1 |
| GBM thickening | (+) | (-) | (+) |
| Bubbling/spike appearance | (+) | (-) | (-) |
| Mesangial proliferation | (-) | (-) | Mild |
| Interstitial lymphocyte infiltration | ND | Mild | Mild |
| Tubular atrophy | ND | Mild | Mild |
| Interstitial fibrosis | ND | Mild | Mild |
| Vascular alterations | ND | Moderate | Moderate |
| Immunofluorescence microscopy | IgG | (-) | (-) | (-) |
| IgA | (+) | IgA1/IgA2 (+)/(-) | (+) |
| IgM | (-) | (-) | (-) |
| κ/λ | (+)/(+ | (+)/(+ | +(+) |
| C3 | (-) | Trace-positive | (-) |
| C1q | (-) | (-) | (+) |
| PLA2R | ND | (-) | (-) |
| Electron microscopy | Subepithelial granular deposits (MN stage) | (+) (I to II) | (+) (early) | (+) (early) |
| Subendothelial granular deposits | (-) | (-) | (-) |
| Mesangial granular deposits | (-) | (-) | Mild |

CHD: coronary heart disease, GBM: glomerular basement membrane, HPF: high-power field, MN: membranous nephropathy, ND: not determined, PLA2R: phospholipase A2 receptor, PSL: prednisolone, RBC: red blood cell, T2DM: type 2 diabetes mellitus, TAC: tacrolimus
from asymptomatic, microscopic hematuria to full-blown acute nephritic syndrome characterized by red to brown urine, proteinuria, edema, hypertension and acute kidney injury. We should also mention that clinical evidence concerning infection was not detected in the skin, respiratory or gastrointestinal systems in our case. Furthermore, classical PIGN always involves C3 and IgG or sole C3 deposition, which is helpful for differentiating PIGN from the condition in our current case based on histological characteristics (14). Another variant that should be differentiated is IgA-dominant acute postinfectious glomerulonephritis (APIGN). IgA-dominant APIGN always occurs in association with Staphylococcal infection and manifests as severe acute kidney injury, proteinuria and hematuria, with IgA being the sole or dominant immunoglobulin on immunofluorescence (15). However, our current case and the other two previously reported patients showed no evidence of concurrent infection, even after long-term surveillance with various examinations. Therefore, the diagnosis of IgA-dominant APIGN could not be established in any of these three patients.

In addition, a review of the literature revealed several unusual case reports of IgA-type monoclonal immunoglobulin deposition disease (MIDD), which is morphologically similar to MN but contains immunoglobulins derived from single B-cell clones. Miura et al. (16) described a case of solitary IgA1-λ deposition in a granular pattern along the glomerular capillary walls in a patient with chronic hepatitis C viral infection, and Kitazawa et al. (17) presented another unusual case of MIDD with IgA1-λ, positively stained by λ-light chains on immunofluorescence on a renal biopsy with membranous features. Intriguingly, Sethi (18) described a monoclonal IgA-type MN patient with diffuse granular deposition of IgA-κ along the glomerular capillary walls in a renal biopsy, which was deemed monoclonal gammopathy with an undetermined underlying etiology. However, despite the similar membranous features among monoclonal IgA-type MN, IgA-type MIDD and MN with solitary IgA deposition, the coexistence of κ- and λ-light chains on immunofluorescence not only highlights the polyclonal origin of the IgA immune deposits in our current observation and the two previous cases but also makes the diagnosis of monoclonal IgA-type MN or IgA-type MIDD unlikely.

In conclusion, IMN associated with solitary polyclonal IgA deposition is an extremely rare entity. Our current case and the two previously reported cases highlight the unique pathological nature of this entity, and future studies of similar cases are needed to outline the potential utility of these findings in guiding personalized therapy.

Written informed consent was obtained from the patient for the publication of this case report, including clinical information and related images. The consent form has been stored by the corresponding author and may be obtained on request from the editor of this journal.

The authors state that they have no Conflict of Interest (COI).

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