CASE REPORT

Membranous Nephropathy with Solitary Immunoglobulin A Deposition

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Abstract

A 71-year-old woman was admitted with nephrotic syndrome. Light and electron microscopic analyses of renal biopsy tissue showed typical diffuse membranous features. In contrast, granular deposition of immunoglobulin A (IgA), but not IgG, IgM, C3 or C1q, was observed along the capillary walls on immunofluorescence. The patient was pathologically diagnosed with diffuse membranous nephropathy with solitary IgA deposition. Secondary membranous nephropathy was suspected; however, no underlying cause was found. The clinical and pathological findings, except for those of immunofluorescence, were all compatible with a diagnosis of primary membranous nephropathy. This is the first reported case of membranous nephropathy associated with solitary IgA deposition.

Key words: IgA deposition, membranous nephropathy

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Introduction

Membranous nephropathy is an immune-complex type of glomerulonephritis accompanied by nephrotic syndrome. Membranous nephropathy is most commonly idiopathic, although it may occur secondary to other conditions. Secondary forms, which account for approximately 25% of cases of membranous nephropathy, are sometimes associated with autoimmune disease, infection malignancy and drugs (1). The pathological findings of membranous nephropathy are characterized by predominant immunoglobulin G (IgG) and/or C3 deposition. Secondary forms of membranous nephropathy, such as membranous lupus nephritis, should perhaps be taken into consideration when IgG and C3 deposits are accompanied by deposits of other types of immunoglobulin or complement, as represented by immunoglobulin A (IgA) and/or C1q. We hereby report a very rare case of membranous nephropathy associated with solitary IgA deposition. The underlying cause, including connective tissue disease, infection and/or cancer, which sometimes manifests later in patients with membranous nephropathy, remains to be defined, even after long-term surveillance with various examinations.

Case Report

A 71-year-old Japanese woman developed generalized edema and was treated with diuretics. Three months later, she was admitted to our hospital with a diagnosis of nephrotic syndrome. The patient had experienced no infectious episodes before admission. She had a history of gastric cancer treated with distal gastrectomy at 57 years of age and hypertension since 58 years of age. Her regular medications on admission included dipyridamole, vitamin B complex, rebamipide and rilmazafone. A physical examination was unremarkable, except for swelling of the lower extremities, and a urinalysis showed proteinuria ³⁺, daily 4.8 g, occult blood ¹⁺, 5-9 red blood cells/high-power field in the sediment. Laboratory studies revealed normocytic anemia at a level of 10.3 g/dL, and serum chemistry showed a blood urea nitrogen level of 20.4 mg/dL, serum creatinine level of 0.8 mg/

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Figure 1. Light microscopy and immunofluorescence in the present case. (a) Light microscopy showed a bubble-like appearance of the glomerular basement membrane (a: arrows, periodic acid-methenamine silver staining) without cellular proliferation. (b-d) Fine granular immunofluorescence with anti-IgA was found along the peripheral capillary walls (b: high-magnification image in c), although no immunofluorescence was seen for anti-IgG (d).

dL, low total serum protein level of 4.7 g/dL, albumin level of 2.1 g/dL, and cholesterol level of 246 mg/dL, which indicated a diagnosis of nephrotic syndrome. In addition, immunological tests showed normal levels of serum IgG, IgA, C3 and C4 (1,030 mg/dL, 271 mg/dL, 147 mg/dL and 32 mg/dL, respectively), and anti-nuclear antibodies were negative. Serum tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9 and alpha-fetoprotein, were all negative, as were serologic tests for hepatitis B surface antigens and hepatitis C antibodies. No urinary Bence-Jones proteins were detected. Meanwhile, a chest computed tomography scan showed a post-inflammatory shadow in the right middle lobe, whereas renal ultrasound disclosed normal kidneys and gastric fiberscopy demonstrated no evidence of recurrence of gastric cancer. As described above, none of the examinations suggested a distinct cause of nephrotic syndrome.

We subsequently obtained the patient’s informed consent to perform a percutaneous renal biopsy. Twelve glomeruli, including a sclerosed glomerulus, were observed on light microscopy. Diffuse thickening of the glomerular capillary wall was seen on periodic acid-Schiff staining, and a bubble-like appearance of the glomerular basement membrane (Fig. 1a, arrows) was recognized on periodic acid-methenamine-silver staining. No mesangial cell proliferation, mesangial accentuation, segmental lesions, including those with nodular features, or amyloid deposition were noted. Meanwhile, on direct immunofluorescence studies (FITC conjugated anti-IgG F0202, IgA F0204, IgM F0203, kappa F0198, lambda F0199: rabbit polyclonal, Dako Japan, FITC conjugated anti-C3 #55167, C1q #55166, C4 #55168: goat polyclonal, MP-Biomedicals, LLC-Cappel Products), all three glomeruli showed fine granular deposits of anti-IgA along the capillary walls (Fig. 1b, c). The immune deposits of IgA had a polyclonal origin, as both anti-kappa and lambda light chain immunofluorescence was positive. In contrast, immunofluorescence was negative for anti-IgG (Fig. 1d), IgM, C3, C1q and C4. Direct immunofluorescence tests were performed more than three times. Electron microscopic examinations of paraffin-embedded materials showed no mesangial widening or hypercellularity (Fig. 2a). Diffuse subepithelial electron-dense deposits (EDDs) were apparent (Fig. 2b); however, no mesangial or subendothelial electron-dense deposits, punctate powdery formed deposits, organized deposits or amyloid fibrils were detected (Fig. 2c). The subepithelial deposits corresponded to Ehrenreich and Churg stage I to II. Based on these findings, membranous nephropathy with solitary IgA deposition was pathologically diagnosed.

According to the fact that only granular deposits of anti-
IgA along the capillary walls were recognized on the immunofluorescence studies, we hypothesized that the membranous nephropathy had developed secondarily to connective tissue disease, infection or cancer. However, exhaustive screening tests to find the underlying cause yielded no clues. During the course of treatment, six months of oral glucocorticoid therapy induced complete remission (prednisolone, 25 mg daily for eight weeks, then gradually tapered for two years). Five years after achieving complete remission, approximately 2 g of proteinuria daily appeared and subsequently continued for three years. During the follow-up period, no serum monoclonal immunoglobulin was detected and serum-free light chain was normal (kappa/lambda rate: 1.38). We have continued to follow the patient for eight years after the diagnosis in order to clarify the possible association between the nephropathy and connective tissue disease, infection or cancer. Nevertheless, no definitive cause has yet been identified.

## Discussion

Based on the fact that other causes should be suspected when IgG deposits are accompanied by IgA deposits, we made various attempts to find the cause of the putative secondary membranous nephropathy. Despite eight years of such efforts, the results of all examinations excluded the possible existence of autoimmune disease, infection and malignancy. Moreover, all pathological findings, except those for immunofluorescence, demonstrated features of primary membranous nephropathy. Light microscopy showed no mesangial cell proliferation, mesangial accentuation, endocapillary proliferation, mesangial deposits or subendothelial deposits, and electron microscopy detected no subendothelial, mesangial or paramesangial deposits. The spatial and temporal distribution of subepithelial deposits was homogenous. In sum, light and electron microscopic examinations conducted to determine the cause of the putative secondary membranous nephropathy yielded no results. Consequently, the present case was judged to be primary membranous nephropathy.

Two of the previously reported cases of IgA-type monoclonal immunoglobulin deposition disease (MIDD) involved membranous features (2, 3). For example, Sethi reported a case of membranous nephropathy associated with monoclonal IgA-kappa deposits and crescents (2), while Miura et al. reported a case of chronic hepatitis C viral infection and rectal cancer that presented with IgA1-lambda-type membranous deposition on a renal biopsy (3). Contrary to that observed in the current case, in which the patient showed characteristics of idiopathic membranous nephropathy, both the patients reported by Sethi and Miura demonstrated histologic features associated with secondary forms. In Sethi’s case, light microscopy revealed cellular crescents, which is unlikely to be reflective of primary membranous nephropathy, and electron microscopy disclosed subepithelial organized deposits (a fine tubular substructure), which is usually associated with paraproteins. Miura’s patient exhibited an increase in the mesangial matrix with mild cellular proliferation on light microscopy in addition to intramembranous EDDs on electron microscopy. These findings, except for those of immunofluorescence, were different from those noted in our case. In association with IgA-type MIDD, all 12 previous cases of IgA-type MIDD were proven to involve monoclonality using anti-light chain staining of renal biopsy tissues (2.3, other references not shown). That is, although we could not determine the IgA subclass pattern, the results of anti-light chain staining were adequate to verify monoclonality in this case. In addition, our patient did not exhibit any typical findings of MIDD, such as nodular lesions on light microscopy or subendothelial powdery formed deposits or amyloid deposits on electron microscopy.

The following describes the results of a comparative review of membranous nephropathy and IgA nephropathy.

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**Figure 2.** Electron microscopy in the present case. (a) No mesangial widening or hypercellularity were noted on a low-magnification view (arrows). (b) The findings showed diffuse subepithelial electron dense deposits. (c) No deposits were found in several areas of the mesangium.
Obtaining a definitive diagnosis of membranous nephropathy requires the detection of pathological findings with granular IgG deposition. In addition to this essential factor, 1-54% of cases of membranous nephropathy are reportedly accompanied by IgA deposition (4). The underlying cause may be suspected when IgG deposits co-exist with IgA deposits. The diagnosis of IgA nephropathy, on the other hand, necessitates the presence of mesangial IgA deposits. Subepithelial deposition is recognized in approximately 13.7% of IgA nephropathy, although it is always accompanied by mesangial deposition (5). The characteristic immunofluorescence findings in the present case are not consistent with either of these previously reported histological features.

With respect to the immune deposit characteristics in this case, the absence of C3 deposition may have great significance. According to previous results of C3 deposition in cases of membranous nephropathy, C3 deposition (78%) is more frequent than that of IgA (20%) and IgM (35%) (4). As for IgA nephropathy, C3 deposition (92.6%) is more frequent than that of IgG (45.8%) and IgM (53.7%) (5). That is, membranous nephropathy and IgA nephropathy are not always necessarily accompanied by complement deposition. In fact, we experienced cases of membranous nephropathy without complement deposition. In a previous experiment using rats, dimeric or polymeric IgA activated the complement pathway, whereas monomeric IgA did not (6). The deficit in complement deposition is possibly related to the mechanism underlying the onset of solitary IgA deposition. It appears that monomeric IgA deposition had a greater impact in this case than that of dimeric or polymeric IgA. Moreover, in determining the site of immune complex deposition, antibody avidity is thought to play a significant role. Previous studies have revealed that higher avidity antibodies are associated with mesangial immune deposits, while lower avidity antibodies form capillary wall deposits (7-9). The same mechanism can be applied to the clinical course: immune deposits of IgG are estimated to localize in the capillary wall, while those of IgA in the mesangium. This case, however, completely contradict these previously established hypotheses. In this context, we see two possible explanations for the pathogenesis of this case. As mentioned above, one is the possible relevance of monomeric IgA, not the commonly observed dimeric form. The other is the existence of corresponding antigens to IgA in the capillary wall, including glomerular podocytes. In other words, antigens acting like phospholipase A2 receptor, alpha-enolase, aldose reductase and manganese superoxide dismutase, which have been previously reported in patients with primary membranous nephropathy (10-12), or bacterial antigens associated with IgA nephropathy (13, 14) may have been present. All things considered, we believe this case calls into question the established theories and may contribute to clarifying the mechanisms of development of immune complex glomerulonephritis.

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

References