Case Report

Development of IgA nephropathy 14 years after diagnosis of membranous nephropathy

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Introduction

Membranous nephropathy is characterized clinically by nephrotic proteinuria and pathologically by the presence of electron dense IgG deposits below the epithelium in glomerular basement membrane. Although about 20–30% of cases of membranous nephropathy are secondary, the majority of cases are idiopathic. The clinical features of IgA nephropathy include haematuria and proteinuria. Although IgA nephropathy is frequently accompanied by IgG and C3 deposits on histopathological examination, IgA deposits are observed predominantly in the mesangial area. The exact pathogenic mechanisms of membranous nephropathy and IgA nephropathy have not yet been fully identified. Several cases of overlapping membranous and IgA nephropathy have been reported [1–8], but the diagnosis of both conditions was made simultaneously on renal biopsy. Therefore, it is not clear whether the two diseases develop simultaneously or at different time points. In this report, we describe a 57-year-old female patient who developed IgA nephropathy 14 years after being diagnosed with membranous nephropathy.

Case

The patient was a 57-year-old female who had no family history of renal diseases, but the father had stomach cancer. She had been healthy except for appendicitis at 19 years of age. In 1966, she was incidentally found to have proteinuria at a routine health check, but this was not further investigated and no treatment was provided. In January 1981, proteinuria was identified again, together with systemic oedema, which worsened gradually. In November 1981, nephrotic syndrome was suspected and the patient was admitted to our hospital on December 25, 1981. On admission, blood pressure was 196/96 mmHg. Urinalysis showed proteinuria (14 g/day) without haematuria. Red blood cell count was 423*10^4/μl, haemoglobin 10.3 g/dl, leukocyte count 8100/μl, platelet count 21*10^4/μl, BUN 10 mg/dl, serum creatinine 0.9 mg/dl, and total cholesterol 335 mg/dl. Blood chemistry showed total protein of 4.3 g/dl, albumin 2.2 g/dl, IgG 324 mg/dl, IgA 213 mg/dl, and IgM 74 mg/dl. Creatinine clearance was 65 ml/min. Liver function tests showed AST 24 U/l and ALT 12 U/l. HBs antigen and HBs antibody were negative. Based on these findings, nephrotic syndrome was diagnosed and treatment with 40 mg/day prednisolone commenced on January 12, 1982.

As the treatment was not effective for massive proteinuria, renal biopsy was performed on April 16, 1982. Light microscopy showed thickening of glomerular basement membrane without proliferation of mesangial cells or matrix expansion in PAS staining (Figure 1a) but spike formations were observed in some parts of the basement membrane in PAM staining. Immunofluorescence examination showed the fine granular depositions of IgG at the basement membrane, slightly positive for IgM and C3, but negative for IgA. On electron microscopy, both dense and lucent deposits were identified below the epithelium of the basement membrane. Based on the above findings, the diagnosis was established as membranous nephropathy, stage II–III. In addition to prednisolone, treatment with 100 mg cyclophosphamide was initiated on May 13, which resulted in a gradual improvement of proteinuria. From February 1984, urinalysis became negative and no abnormalities were detected. Following the induction of a complete remission, she was
admitted for the second histopathological examination in October 1984. On the second admission, BUN was 12 mg/dl, serum creatinine 0.8 mg/dl, and total cholesterol 175 mg/dl. Total protein was 6.5 g/dl, albumin 4.2 g/dl, IgG 1062 mg/dl, IgA 402 mg/dl, IgM 52 mg/dl, AST 14 U/l, and ALT 15 U/l. The second renal biopsy was performed on October 29, 1984. Light microscopy showed no spike formation at the basement membrane by PAM staining, and no proliferation of mesangial cell or matrix expansion in PAS staining (Figure 1b). Tissue sections stained by immunofluorescence methods were slightly positive for IgG and C3, but negative for IgA. Electron microscopy showed translucent subepithelial deposits at the basement membrane and a partially normal basement membrane. These findings were compatible with the diagnosis of stage IV membranous nephropathy. Treatment with steroid was continued until August 1992. No abnormalities were found on urinary examination until October 1994, when proteinuria was detected.

Fig. 1. (a) Light microscopy showed thickening of glomerular basement membrane without proliferation of mesangial cells or matrix expansion in PAS staining (magnification ×240). (b) Light microscopy showing no proliferation of mesangial cell or matrix expansion in PAS staining (magnification ×240). (c) Light microscopy showing mild to moderate proliferation of mesangial cells and matrix, and PAS-positive deposits in the mesangial area in PAS staining (magnification ×240). (d) Immunofluorescence microscopy showing coarse granules for IgA mainly in the mesangial area (magnification ×240).
followed by a gradual increase in the degree of proteinuria. In June 1996, treatment with 0.5 mg betamethasone was restarted. However, as urinary abnormalities did not improve, the dose was increased to 2 mg in August 1996. Furthermore, as urinary occult blood became positive, she was admitted for the third time on October 17, 1996. Blood pressure was 116/74 mmHg. Urinalysis was positive for occult blood and proteinuria, quantified at 0.6 g/day, but negative for glucose. Red blood cell count was 445 × 10^6/mm³, haemoglobin 13.5 g/dl, leukocyte count 7900/mm³, platelet 15 × 10^9/mm³, BUN 15 mg/dl, serum creatinine 0.7 mg/dl, and total cholesterol 232 mg/dl. Total protein was 5.6 g/dl, albumin 3.3 g/dl, IgG 977 mg/dl, IgA 344 mg/dl, and IgM 77 mg/dl. Creatinine clearance was 63 ml/min. AST was 16 U/l, ALT 25 U/l, and CA19-9 was 45.4 U/ml. Blood glucose was 76 mg/dl, and HbA1c was 5.7%. Anti-hepatitis C virus (HCV) antibody titre was 1.8 (normal range, <1.0). The third renal biopsy was performed on October 23, 1996. On light microscopy, mild to moderate proliferation of mesangial cells and matrix expansion were detected in PAS stained sections, and PAS-positive deposits were observed in the paramesangial area (Figure 1c). Some glomeruli showed global sclerosis, segmental sclerosis or fibrocellular crescent formation. Cellular infiltration was observed locally in the interstitium. Immunofluorescence examination showed fine granular deposits of IgG mainly in the basement membrane, coarse granules of IgA mainly in the mesangial area (Figure 1d), and slightly positive staining for IgM, C3 at the mesangial area. On electron microscopy, diffuse dense deposits were noted at the mesangial area and basement membrane, and some of them were buried in the basement membrane. Based on these pathological features, the patient was diagnosed with membranous nephropathy at stage II–III with overlapping IgA nephropathy.

Discussion

We reported here a patient with IgA nephropathy occurring 14 years after the diagnosis of membranous nephropathy. As membranous nephropathy is classified into idiopathic and secondary, it is important to examine the causes of secondary membranous nephropathy. When membranous nephropathy was diagnosed 14 years earlier, our patient did not show any abnormalities other than nephrotic syndrome and hypertension. Therefore, membranous nephropathy was classified as idiopathic. However, the possibility of secondary membranous nephropathy could not be completely excluded, because the patient was weakly positive for anti-HCV antibody on the third admission. As the examination of antibody against HCV was not available during the first and second admissions, it is not clear when our patient was infected by HCV. HCV causes several types of renal diseases [9]. However, almost all patients with HCV-associated nephropathy have liver dysfunction and the titre of anti-HCV antibody was very low in our patient, suggesting that HCV was not associated with membranous nephropathy in this case. CA19-9 was slightly increased, but there were no abnormalities of the gallbladder, liver or pancreas on abdominal CT and echography. Furthermore, gastric endoscopy and colon irrigoscopy showed no abnormalities. With regard to IgA nephropathy systemic disease, such as systemic lupus erythematosus, rheumatoid arthritis, and diabetes mellitus (which cause mesangial proliferative glomerulonephritis and IgA deposition) were excluded. Based on these findings, our patient had primary membranous nephropathy and IgA nephropathy.

To our knowledge, more than 10 cases of overlapping membranous and IgA nephropathy have been reported, including suspected cases [1–6]. In these reports, the onset of each nephropathy was unknown as the two nephropathies were discovered on the first renal biopsy. Doi et al. [1] reported three such cases and postulated that both renal diseases were caused by one common mechanism. In their patients as well as those of Kobayashi et al. [7], different immunoglobulins were deposited in different sites according to the molecular size of these molecules. IgG, which is a small molecule, may deposit on the basement membrane and relatively large IgA may deposit in the mesangial area. In the present case, three renal biopsies were obtained during a 14-year observation period, but only membranous nephropathy was diagnosed on the first and second biopsies, while the diagnosis of IgA nephropathy, in addition to membranous nephropathy, was established in the last biopsy, which was performed 12 years after the second biopsy. Our patient is the first case of IgA nephropathy overlapping with membranous nephropathy during the clinical course. It is important to determine when IgA nephropathy develops in such condition. Although it is often difficult to clarify when IgA nephropathy develops, it was assumed to have occurred in 1995 when urinary occult blood became positive.

Another important aspect of our case presentation is why the two renal diseases occurred in the same patient. Although it is difficult to consider that the cause of membranous nephropathy later induced IgA nephropathy, changes in the serum IgA level are interesting in our patient. The level of serum IgA was 213 mg/dl in the first admission and increased to 402 and 344 mg/dl during the second and third admission, respectively. Although high serum IgA level is not specific to IgA nephropathy, 315 mg/dl of serum IgA is the diagnostic criterion for IgA nephropathy [10]. Certain factors, such as increased IgA production, might have been involved in the development of IgA nephropathy between the first and second admission. As betamethasone and cyclophosphamide are immunosuppressants, it is also possible that discontinuation of these drugs in 1992 might have enhanced IgA synthesis, inducing IgA nephropathy. As to the antigen causing renal diseases, it remains unknown whether
in IgA nephropathy it is the same or different from that involved in membranous nephropathy. Moreover, Jennette et al. [2] reported brothers with overlapping IgA and membranous nephropathy, which implies that some genetic factors might be associated with both conditions. Familial forms of both nephropathies [11,12] have been reported, indicating that some common genetic factors may be associated with these two renal diseases. Previous studies indicated that IgA nephropathy was associated with HLA-DR4 [13], HLA-B35 [14], and HLA-DR2 [11] and that membranous nephropathy was associated with HLA-DR2 [13], HLA-DR3, and HLA-B8 [15]. However, our patient was typed as HLA-B7, B62, DR8, DR15, showing no relation to the above HLA types. Further studies of the aetiology of these overlapping renal diseases may reveal the cause of each nephropathy.

References


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