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A case of minimal change nephrotic syndrome with IgA nephropathy transitioned to focal segmental glomerulosclerosis

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Patient was a 50-year-old woman. After experiencing lower-extremity edema from September 1999, her weight increased by 5 kg in one month and she was admitted to our hospital with suspected nephrotic syndrome. Urine protein level was 3.5 g per day; erythrocytes in urine 10–15 /HPF; and serum albumin level 2.5 g/dl. Furthermore, an accumulation of pleural effusion was confirmed on chest X-ray. The results of a renal biopsy indicated slight mesangial proliferation in the glomeruli by light microscope, and the immunofluorescence study confirmed the deposition of IgA and C3 in the mesangial area. Diffuse attenuation of foot processes and dense deposits in the mesangial area were observed by electron microscopy. Treatment with 40 mg/day of prednisolone was effective, and proteinuria was negative one month later. Because of this course, we diagnosed as minimal change nephrotic syndrome complicated by mild-proliferative IgA nephropathy. In November 2000, there was a relapse of nephrotic syndrome, which was believed to be induced by influenza vaccinations, but response to treatment with steroid increase was favorable, and proteinuria disappeared on day 13 of steroid increase. A second relapse, occurred in May 2001, showed steroid-resistance with renal insufficiency, and selectivity index increased to 0.195. By light microscope, focal sclerotic lesions of the glomeruli were observed, and the immunofluorescent study revealed the attenuation of mesangial IgA and C3 deposition. These findings led to the diagnosis that minimal change nephrotic syndrome had transitioned to focal segmental glomerulosclerosis, wherein mesangial IgA deposition was reduced with immunosuppressive treatment. Renal function gradually worsened subsequently, to the point of end-stage renal failure by 27 months after the second relapse of nephrotic syndrome.
Introduction

Mesangial proliferative glomerulonephritis is a syndrome characterized by the proliferation of glomerular mesangial cells and an increased mesangial matrix; IgA nephropathy is a representative disease. In IgA nephropathy, IgA deposition in the mesangial area can be observed by immunofluorescence microscopy and is accompanied by depositions of C3, IgG, IgM, and fibrinogen. Although IgA nephropathy is characterized by hematuria and accompanying proteinuria in urine tests, nephrotic syndrome is rare (3.7–7.0%) [1]. In addition, the selectivity of proteinuria in IgA nephropathy presenting with nephrotic syndrome is low, and generally nephrotic syndrome in IgA nephropathy is resistant to steroid therapy [1].

Several cases have been reported that presented with minimal change nephrotic syndrome in clinical findings, with confirmation of IgA depositions in the mesangial area by the fluorescent study [2-7]. The pathological conditions thereof have been considered to be as follows: (1) IgA nephropathy with nephrotic syndrome, (2) a combination of minimal change nephrotic syndrome and IgA nephropathy, or (3) an observation of nonspecific IgA depositions in minimal change nephrotic syndrome. However, it has been difficult to clearly differentiate between these conditions.

On the other hand, some patients with minimal change nephrotic syndrome who showed a favorable response to steroid treatment have later become resistant to therapy, leading to a diagnosis of segmental glomerulosclerosis by renal biopsy. In a study of 65 patients with a histological diagnosis of minimal change nephrotic syndrome [8], six out of the seven cases that had undergone another round of renal biopsy because steroid-resistant minimal change nephrotic syndrome was reported to be presented with focal segmental glomerulosclerosis.

In the present case, we encountered a patient with nephrotic syndrome accompanied by IgA nephropathy diagnosed by a renal biopsy and exhibited a favorable response to steroid treatment, we diagnosed a combination of IgA nephropathy and minimal change nephrotic syndrome. Here, we report a patient underwent an interesting clinical course wherein nephritic
syndrome, with recurring relapses, relapsed for the second time with focal segmental glomerulosclerosis and attenuating IgA deposition with a literature.
**CASE**

Patient was a 50-year-old woman. After experiencing lower-extremity edema from September 1999, her weight increased by 5 kg in one month. After consultation at the nearby clinic, pleural effusion was confirmed by chest X-ray. Hypertension (systolic blood pressure: 190 mmHg), and levels of urinary protein (++++), urinary albumin (++++), serum protein 5.7 g/dl, and serum albumin 3.2 g/dl were determined. This was first time for her to point out the urinary abnormalities. She was referred and admitted to our hospital with suspected nephrotic syndrome on October 10, 1999. Physical findings on admission were as follows: height 155 cm; weight 59 kg; body temperature 36.7 °C; blood pressure 188/109 mmHg; and pulse rate 83/min. Neither anemia nor jaundice was confirmed. Lower-extremity edema was observed but there were no abnormal cardiac or breath sounds. Laboratory data have been listed in Table 1. Level of proteinuria was 3.5 g/day, serum protein was 4.7 g/dl, and serum albumin was 2.5 g/dl, thus confirming nephrotic syndrome. Renal function was normal, with creatinine clearance at 93.5 ml/min, and there was no reduction in the levels of complements; antinuclear antibodies were also absent. Serum IgA level was 318 mg/dl. Mild hematuria was observed in urinalysis, with 8–10 visible erythrocytes per high power field, and the selectivity index was 0.136. A renal biopsy showed mild mesangial cell proliferation and increased mesangial matrix in 11 of 14 glomeruli under light microscopy (Fig. 1a). No interstitial changes were observed. IgA (Fig. 1b), IgM, C3 and C1q depositions were observed in the mesangial region by the immunofluorescence microscopy. IgG depositions was not observed. In paramesangial capillary, no deposits were observed. Diffuse attenuation of foot processes and dense deposits in the mesangial region were identified by electron microscopy (Fig. 1c). These findings led to the suspecting either mild-proliferative IgA nephropathy presenting with nephrotic syndrome or minimal change nephrotic syndrome complicated by IgA nephropathy; however, once treatment was initiated with 40 mg/day of prednisolone, proteinuria and hematuria disappeared one month later. Since response to steroids as a clinical course was favorable, we diagnosed a combination
of minimal change nephrotic syndrome and IgA nephropathy. Moreover, because steroid-induced diabetes has been caused by the use of steroids, she was treated with voglibose and then discharged.

In the outpatient course, her urinalysis remained negative for proteinuria and hematuria, and prednisolone was tapered to 10 mg/day. However, in November 2000, she had proteinuria 10 days after an influenza vaccination. She also had an onset of lower-extremity edema beginning from around January 2001, and serum albumin level gradually dropped to 2.4 g/dl. She had no skin lesion. Thus, on February 9th of the same year, she was admitted to our hospital for the second time with a diagnosis of relapsed nephrotic syndrome. Urinalysis on admission indicated a proteinuria level of 5.5 g/day, which indicated nephrotic syndrome. In addition, the selectivity index was 0.125. The drug lymphocyte stimulation test for the influenza vaccine was positive, and since there have been reported [9] that kidney diseases such as crescentic glomerulonephritis and focal segmental glomerulosclerosis occurred after administration of an influenza vaccine, a second renal biopsy was performed. Renal biopsy results showed mild mesangial proliferative nephritis in 13 of 15 glomeruli, and the findings were almost identical to those of the first renal biopsy, including IgA, IgM and C3 depositions observed in the mesangial area with the immunofluorescence microscopy. IgG and C1q depositions were not observed. In paramesangial capillary, no deposits were observed. The sample for electron microscopy included no glomeruli. Based on these findings, we considered that minimal change nephrotic syndrome had relapsed, triggered by the influenza vaccine. Given that the patient feared worsening of steroid-induced diabetes and expressed the desire to reduce the amount of prednisolone, 500 mg/day of methylprednisolone was administered for 3 days intravenously followed by 30 mg/day of prednisolone orally. Response to steroid treatment was favorable at this time as well, and proteinuria was negative by day 13 after treatment.

During the outpatient course observation, urinalysis remained negative for proteinuria, and prednisolone was reduced to 15 mg/day, but in May 2001, nephrotic syndrome was
confirmed to have relapsed with no clear cause. Proteinuria was almost identical to that during previous onsets (4.7 g/day), but the selectivity index increased to 0.195, which was a change from previous findings. Because the patient rejected increasing prednisolone by oral administration, a 3-day intravenous drip of 500 mg/day of methylprednisolone was started for the second time; however, proteinuria level was not reduced. Moreover, serum creatinine level, which had transitioned to around 0.7 mg/dl, had now increased to 1.0 mg/dl, and she was admitted to our hospital for the third time. Because nephrotic syndrome, which had been observed up to this point, was now resistant to steroids, we speculated that minimal change nephrotic syndrome had transitioned to focal segmental glomerulosclerosis. Thus, a third renal biopsy was performed with the objective of determining the diagnosis and the future course of treatment. In renal biopsy, five of the 35 glomeruli exhibited focal sclerotic disease under light microscopy (Fig. 2a), and two sclerotic glomeruli were observed. In many of the other glomeruli, mild mesangial proliferation was same extent as those in the first or second biopsies. Localized fibrosis and cellular infiltration were confirmed in the interstitium. The IgA and C3 depositions in the mesangial region were clearly reduced from the time of the second renal biopsy as observed by the immunofluorescence microscopy (Fig. 2b), and IgG, IgM, C3 or C1q depositions were not observed. The dense deposits in the mesangial region that had been confirmed during the first renal biopsy were not found under electron microscopy this time, and only diffuse attenuation of foot processes were observed. Based on the above results, we diagnosed focal segmental glomerulosclerosis. After treatment with steroids, immunosuppressive agents including mizoribine and cyclosporine, and LDL apheresis, proteinuria level was reduced to 2.5 g/day by April 2002, and the patient was discharged. Fig.3 showed clinical course.

However, remission was not observed in the period following discharge, and proteinuria level increased up to 10 g/day, indicating that the pathological state of steroid-resistant nephrotic syndrome persisted. Renal function worsened from November 2002 onward, and she started maintenance hemodialysis in February 2004.
Discussion

It is rare for nephrotic syndrome caused by IgA nephropathy (3.7–7.0%) [1], and such cases generally show active hematuria and low-selectivity proteinuria, renal dysfunction, hypertension, and resistance to treatment; they are very often accompanied by tissue modifications like crescentic formation or Bowman’s capsule adhesion. On the other hand, there have been several reported cases of patients presenting with nephrotic syndrome showing favorable response to steroid treatment, which indicated mild or no glomerular abnormalities in renal biopsy by light microscopy, and IgA depositions in the mesangial region observed with the immunofluorescence microscopy [2-7]. These reports have therefore included the following conditions: (1) nephrotic-type IgA nephropathy, (2) a combination of minimal change nephrotic syndrome and IgA nephropathy, and (3) nonspecific IgA depositions observed in minimal change nephrotic syndrome. However, differentiating between each of these conditions is difficult and inconclusive.

Mustonen et al.[2] in their report on nephrotic-type IgA nephropathy reported eight out of 170 cases of IgA nephropathy patients presented with nephrotic syndrome. The renal biopsy specimens of three patients showed minimal or mild mesangial alterations, and the other five biopsies showed moderate to marked mesangial changes with segmental sclerosing or proliferative lesions. The three patients with mild glomerular alterations had normal kidney function and showed steroid-response nephrotic syndrome, whereas those with moderate glomerular changes or worse showed poor response to steroid treatment, accompanied by renal dysfunction. However, generally when nephrotic syndrome is presented with IgA nephropathy, it is often accompanied by treatment resistance, or tissue changes like crescentic formations or Bowman’s capsule adhesions. Thus, only on the basis of the favorable response to steroid treatment from patients like the present case with mild tissue changes, it is difficult to conclude that our patient was a case of nephrotic-type IgA nephropathy.
Nagata et al.[3] reported a combination of minimal change nephrotic syndrome and IgA nephropathy. On the first episode of nephrotic syndrome, renal biopsy revealed minimal change nephrotic syndrome. At the time of fourth relapse, hematuria and mesangial IgA depositions in renal biopsy were observed, so they conclude that IgA nephropathy had been complicated by minimal change nephrotic syndrome. Lai et al.[4] also reported a study of eight patients presented with minimal change nephrotic syndrome diagnosed by light microscopy with confirmation of IgA depositions in the mesangial region, showing an increase in serum IgA level in 60% patients, hematuria in 50%, and hypertension in 25%; however, these patients showed a favorable response to steroid treatment. It is difficult to clearly determine whether minimal change nephrotic syndrome has been complicated with IgA nephropathy. The pathological findings of our patient indicated mild-proliferative IgA nephropathy, but it was difficult to consider this to be the cause of nephrotic syndrome; furthermore, given the favorable response to steroid treatment and the clinical course, we considered that the present case was a combination of minimal change nephrotic syndrome and mild-proliferative IgA nephropathy.

IgA depositions in the mesangium are common and have been reported to have been observed in 16.1% of patients in a study on 510 kidney donors [10]; however, in cases of minimal change nephrotic syndrome as well, the observed IgA depositions had been reported to be nonspecific [5-7]. However, pathologically, our patient exhibited mild proliferation but clear IgA depositions, and we considered that it was inaccurate to consider the IgA depositions as nonspecific.

The clinical findings during the third nephrotic syndrome were different from those during the first and second nephrotic syndrome. After the onset of third nephrotic syndrome, she showed resistance to steroids and she started maintenance hemodialysis 27 months after the second relapse. In renal biopsy, IgA deposits were attenuated and focal segmental glomerulosclerosis was diagnosed. In some cases, repeated renal biopsies provided some patients with minimal change nephrotic syndrome failed to respond to treatment with steroids,
and revealed focal segmental glomerulosclerosis. The course of the present case conforms with the same as well. In a study on 65 patients, Waldman et al.[8] reported that these patients had been histologically diagnosed with minimal change nephrotic syndrome; six out of seven cases that had undergone renal biopsy repeatedly for steroid-resistant minimal change nephrotic syndrome had presented with focal segmental glomerulosclerosis, and of these, three reached end-stage renal failure. Both minimal change nephrotic syndrome and focal segmental glomerulosclerosis have some common observed features; (1) they show loss of foot processes and nephrotic syndrome, (2) they have a subgroup of minimal change nephrotic syndrome that includes global sclerosis, and (3) they have lesions that change from minimal change nephrotic syndrome to focal segmental glomerulosclerosis following repeated dosing or a time course in the case where aminonucleoside nephrosis is used as a model of nephrotic syndrome [11].

Therefore, both minimal change nephrotic syndrome and focal segmental glomerulosclerosis are considered to be in the category of podocytopathy now. However, there are major differences in clinical histopathology between minimal change nephrotic syndrome and focal segmental glomerulosclerosis; impairment of foot processes in patients with minimal change nephrotic syndrome is reversible, whereas focal segmental glomerulosclerosis is associated with detachment of podocytes or vacuolar degeneration in which the lesion eventually becomes irreversible. As shown in this case, the shift from minimal change nephrotic syndrome to focal segmental glomerulosclerosis may involve a mechanism whereby podocyte injury caused by the onset of minimal change nephrotic syndrome is associated with elevated glomerular pressure or increased glomerular filtration rate (GFR), due to any reason, followed by glomerular hypertrophy. This results in increased tension per podocyte, leading to podocyte detachment, which thereby contributes to a sclerosing lesion [12]. In other words, it is thought that the sites where podocytes are detached are coated by epithelial cells lining Bowman's capsule that induce production of the extracellular matrix followed by a sclerosing lesion, and that this may lead to focal segmental glomerulosclerosis [13]. A further reported mechanism suggests that podocyte
injury also promotes glomerulosclerosis by decreasing podocyte-derived important factors such as VEGF and angiopoietin-1, that maintain the structure of glomerular capillary loop [14].

Moreover, in retrospect, her selectivity index at a third admission increased to 0.195, but it was not so high as FSGS. Bazzi et al. [15] examined a selectivity index for 29 patients with focal segmental glomerulosclerosis and reported that 7%, 31%, and 62% of the patients had indices of <0.10, ≥0.11 to <0.21, and ≥0.21, respectively. The mechanism underlying the widely varying selectivity index for focal segmental glomerulosclerosis is currently not known but may depend on the degree of podocyte injury in each patient. In our case, mild change in her selectivity index might indicate the histological alteration.

IgA nephropathy exhibiting mild mesangial proliferation in the first and second renal biopsies was observed in our patient. Reduction or disappearance of IgA depositions is not generally observed with IgA nephropathy; however, Yoshikawa et al. [16] reported a IgA nephropathy patient that mesangial IgA deposits became significantly less intense at the end of treatment with steroids and immunosuppressive agents. In a patient with minimal change nephrotic syndrome in whom nonspecific IgA depositions had been observed, it was also reported that disappearance or reduction in IgA depositions was seen after remission of nephrotic syndrome because of treatment [17]. From these reports, we concluded that in the present case, IgA depositions had been reduced by treatment with steroids and immunosuppressive agents. Furthermore, although some glomeruli showed segmental glomerulosclerosis in the third renal biopsy, mesangial cell proliferation and expansion of mesangial matrix had not worsened in the other glomeruli to the same extent as those in the first or second biopsies. Thus, we considered that the worsening of renal function in the present case was not because of the progression of IgA nephropathy, but was caused by a transition from minimal change nephrotic syndrome to focal segmental glomerulosclerosis.

Recently, lesions histologically identical with focal segmental glomerulosclerosis may appear in IgA nephropathy. Karoui et al. [18] reported that 101 out of 128 patients diagnosed
with IgA nephropathy presented with some form of lesion consistent with focal segmental glomerulosclerosis, and this group had significantly worse renal survival at 80 months. Weber et al.[19] reported that out of 72 patients that had been histologically diagnosed with mild IgA nephropathy, 26 patients presented with focal segmental glomerulosclerosis, which had significantly worsened kidney function and lowered serum albumin level, and trended toward decreased renal function as compared to those that had not presented with focal segmental glomerulosclerosis. Based on the clinical course and pathological findings, we considered that minimal change nephrotic syndrome had transitioned to focal segmental glomerulosclerosis as the cause of the third relapse of nephrotic syndrome in our patient; however, we cannot deny the possibility that our patient who exhibited IgA nephropathy presented with focal segmental glomerulosclerosis.

In the present case, the second nephrotic syndrome occurred ten days after inoculation with an influenza vaccine. Systemic side effects of the influenza vaccine are rare, but a paper by Yanai-Berar et al.[9] have summarized their report on renal dysfunction, and Kielstein et al.[20] have reported a patient with an onset of minimal change nephrotic syndrome four days after influenza vaccine administration. In our case, since nephrotic syndrome occurred after ten days of treatment and the drug lymphocyte stimulation test performed on the influenza vaccine was positive, we considered that the influenza vaccine had some effect on the recurrence of nephrotic syndrome. In addition, Yanai-Berar et al.[9] have also reported a case of influenza vaccination induced purpura nephritis, but purpura did not appear in our case, thus we did not diagnose our case with purpura nephritis. Influenza vaccination is highly encouraged currently, and it is necessary to pay very careful attention to relapse of nephrotic syndrome after inoculation with an influenza vaccine.

This is the report of a patient with nephrotic syndrome in whom minimal change nephrotic syndrome and IgA nephropathy occurred in combination. Since nephrotic syndrome had become resistant to treatment by the time of third relapse, renal biopsy diagnosis indicated
that minimal change nephrotic syndrome had transitioned to focal segmental glomerulosclerosis, while IgA depositions had reduced. Treatment resistance persisted thereafter as well, she needed maintenance hemodialysis 53 months after the first onset. However, no treatment method had been established for such a case and therefore we believe that there is a need to perform a study on more such cases in future.

Disclosure

All the authors have declared no competing interest.
References


Fig. 1 Results of first renal biopsy

(a) Low grade mesangial proliferation with slight expansion of the mesangium were observed on light microscopy (periodic acid–Schiff stain, x400). (b) Immunofluorescence study revealed mesangial deposits of IgA. (c) In electron microscopy, diffuse effacement of the epithelial cell foot processes and dense deposits in mesangial areas were observed.
Fig. 2 Results of third renal biopsy

(a) light microscopy showing focal segmental glomerulosclerosis (periodic acid–Schiff stain, x400). (b) The decrease of IgA deposition were observed on immunofluorescence
Fig. 3 Clinical course

Although our patient was in complete remission from the first and second instances of nephritic syndrome with steroid treatment, the patient showed resistance to steroids and immunosuppressive agents at the time of third nephrotic syndrome.

RB: renal biopsy, PSL: prednisolone, m-PSL div: methylprednisolone 500 mg/day for three days, OB: occult blood /F, SI: selectivity index, MZB: mizoribine, CYA: cyclosporin
Table 1. Laboratory data on first admission

<table>
<thead>
<tr>
<th></th>
<th>WBC 5200 /mm³</th>
<th>TP 4.7 g/dL</th>
<th>IgG 708 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seg.</td>
<td>4.15 x10⁶/mm³</td>
<td>ALB 2.5 g/dL</td>
<td>IgA 318 mg/dL</td>
</tr>
<tr>
<td>Lymph</td>
<td>56 %</td>
<td>BUN 14.0 mg/dL</td>
<td>IgM 233 mg/dL</td>
</tr>
<tr>
<td>Mono</td>
<td>28 %</td>
<td>Cr 0.6 mg/dL</td>
<td>IgE 13 mg/dL</td>
</tr>
<tr>
<td>Baso</td>
<td>11 %</td>
<td>UA 2.9 mg/dL</td>
<td>C3 105.0 mg/dL</td>
</tr>
<tr>
<td>Eosion</td>
<td>1 %</td>
<td>Na 144 mEq/L</td>
<td>C4 20.4 mg/dL</td>
</tr>
<tr>
<td>RBC</td>
<td>3 %</td>
<td>K 3.7 mEq/L</td>
<td>ANF (-)</td>
</tr>
<tr>
<td>Hb</td>
<td>13.0 g/dL</td>
<td>Cl 110 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Hct</td>
<td>38.6 %</td>
<td>Ca 8.2 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Plt</td>
<td>25.6 /mm³</td>
<td>IP 3.1 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TC 256 mg/dL</td>
<td>Protein (4+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TG 105 mg/dL</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>AST 7 IU/L</td>
<td>Urine protein 2.9 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALT 8 IU/L</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>LDH 135 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRP 0.10 mg/dL</td>
<td>Selectivity index 0.135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FBS 88 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

|                | Max: 708 | Occult blood (2+) | |
|                | 318      | RBC 8-10 /F       | |
|                | 233      | WBC 10-15 /F      | |
|                | 13       | NAG 13.3 IU/L     | |
|                | 93.5     | Ccr 93.5 ml/min   | |

<Peripheral blood>  <blood chemistry>  <Immunological studies>