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ORIGINAL ARTICLE

Pattern of double glomerulopathy in children

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Abstract Occasional case reports have been issued on children with double glomerulopathy, involving either the coexistence of two different glomerulopathies or superimposition of a second glomerulopathy onto a first. A retrospective clinicopathological review of 294 children who had received renal biopsies resulted in 9 (3.1%) being confirmed to have double glomerulopathy. Superimposed glomerulopathy was diagnosed by a second renal biopsy in two cases, and coexistence of two glomerulopathies was confirmed by single biopsy in seven. Original glomerulopathies were those with a chronic course, such as Alport syndrome, IgA nephropathy, relapsing minimal-change nephrotic syndrome, Frasier syndrome, and thin basement membrane nephropathy. The superimposing glomerulopathies were common types in children, such as postinfectious glomerulonephritis, IgA nephropathy, and Henoch-Schönlein nephritis. Thus, the pattern of double glomerulopathy was considered to be due to the chance occurrence of two different glomerulopathies without a common pathogenesis. Acute nephritic symptoms of superimposed glomerulopathies resolved almost completely during follow-up in most cases. Double glomerulopathies are not rare in children and may occur by chance alone in most cases. The possibility of superimposed glomerulopathy should be suspected if the clinical course of a glomerulopathy changes atypically. However, the long-term influence of a superimposed glomerulopathy on renal functional deterioration remains unclear.

Keywords Double glomerulopathy · Children

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Introduction

Double glomerulopathy describes the coexistence of two different glomerular diseases or superimposition of a second glomerulopathy onto the course of an original glomerulopathy. Occasional reports are available on single cases or a small number of cases of double glomerulopathy. However, systematic reviews of double glomerulopathy have only been performed rarely in adult patients [1, 2], and not in pediatric patients. In addition, it is controversial whether the concomitant occurrence of two apparently unrelated glomerulopathies is a coincidence or a separate entity in glomerular pathology, or whether a superimposed glomerulopathy affects the long-term prognosis of the primary glomerulopathy.

In this study, we performed a clinicopathological review of children with biopsy-proven double glomerulopathy.

Patients and methods

Double glomerulopathy was defined by pathological confirmation of two coexisting different glomerular diseases or superimposition of a second glomerulopathy onto the course of an original glomerulopathy. Double glomerulopathies involving graft kidneys were excluded. The clinicopathological findings of 294 children who had undergone a renal biopsy in Seoul National University Children's

Hospital during the period January 1999 to May 2005 were retrospectively reviewed, and 9 patients (3.1%, 6 boys and 3 girls) with double glomerulopathy were included in this study. The mean age at the diagnosis of double glomerulopathy was 7.2±2.3 years (4–11 years), and two boys were brothers.

Results

Superimposition of a second glomerulopathy was confirmed by a second biopsy in two patients, and the coexistence of two glomerulopathies was detected by a single biopsy in seven. The original disease was Alport syndrome in four cases, IgA nephropathy in two cases, minimal-change nephrotic syndrome in one case, focal segmental glomerulosclerosis associated with Frasier syndrome in one case, and thin basement membrane nephropathy (TBMN) in one case. The superimposed glomerulopathy was poststreptococcal or postinfectious glomerulonephritis (PSGN or PIGN) in five cases, IgA nephropathy in two cases, and Henoch-Schönlein nephritis in two cases (Table 1).

Case 1 and 2 (Alport syndrome+PSGN) Cases 1 and 2 were male siblings, and their mother had persistent microscopic hematuria and (1+) albuminuria. Case 1, the elder brother, developed recurrent gross hematuria at the age of 3 years. In between the episodes of gross hematuria, serial urinalyses revealed microscopic hematuria without proteinuria. At age 7 years, he experienced another episode of gross hematuria followed by a newly developed generalized edema and hypertension. Serum creatinine and albumin were 0.6 mg/dL and 3.0 g/dL, respectively, and urinalysis revealed (3+) albuminuria. This episode was preceded 10 days beforehand by an upper respiratory tract infection. His ASO titer was strongly positive and serum C3 (normal 70–150 mg/dL) and C4 (normal 10–35 mg/dL) levels were 23 and 24 mg/dL, respectively.

A kidney biopsy revealed the ultrastructural changes of glomerular basement membranes (GBM) that are typical of Alport syndrome and the typical subepithelial humps of PSGN (Fig. 1). Pure tone audiometry revealed sensorineural hearing loss in the high-frequency range. Hypertension and edema disappeared completely 2 weeks after presentation, and serum C3 and albumin also normalized. Albuminuria decreased to trace to (1+) amount. Case 2, the 5-year-old younger brother, had similar acute nephritic symptoms at the same time as his brother, and nearly identical renal biopsy findings.

Case 3 (Alport syndrome+PSGN) A 3-year-old girl with incidentally detected microscopic hematuria without proteinuria was clinically diagnosed to have familial nephritis because her mother had persistent microscopic hematuria with intermittent proteinuria. However, 1 year later, PSGN with typical clinical and laboratory features developed. A renal biopsy revealed the typical GBM changes of Alport syndrome with segmental loss of type IV collagen α5 chain expression along the GBM and several subepithelial humps of PSGN. Her acute nephritic symptoms disappeared rapidly on conservative management only, but microscopic hematuria with minimal or no proteinuria persisted thereafter.

Case 4 (Alport syndrome+IgA nephropathy) A 6-year-old girl developed sudden onset gross hematuria, proteinuria (1.7 g/day) and a puffy face. Serum creatinine and albumin were 0.5 mg/dL and 2.6 g/dL, respectively. Renal ultra-

Table 1 Patterns of double glomerulopathy encountered in this study

Case no.	Original disease/superimposed disease	Diagnostic clues, original/superimposed disease	Residuals of superimposed disease
1	Alport syndrome/PSGN	FHx, GBM change/humps, low C3	None
2	Alport syndrome/PSGN	FHx, GBM change/humps, low C3	None
3	Alport syndrome/PSGN	FHx, GBM change/humps, low C3	None
4	Alport syndrome/IgA nephropathy	FHx, GBM change/IgA deposits by IF	N/E
5	IgA nephropathy/PIGN	IgA deposits by IF/humps, low C3	None
6	IgA nephropathy/PI-RPGN	IgA deposits by IF/humps, low C3, crescents	N/E
7	SD-MCNS/HSN	Clinical course, 1st renal biopsy/skin lesions, IgA deposits by IF	Microscopic hematuria
8	Frasier syndrome/HSN	Gene study, 1st renal biospy/skin lesions, IgA deposits by IF	N/E
9	Thin GBM disease/IgA nephropathy	FHx, GBM changes/IgA deposits by IF	N/E

FHx Family history, *GBM* glomerular basement membrane, *HSN* Henoch-Schönlein nephritis, *IF* immunofluorescent microscopy, *PIGN* postinfectious glomerulonephritis, *PI-RPGN* postinfectious rapidly progressive glomerulonephritis, *PSGN* poststreptococcal glomerulonephritis, *SD-MCNS* steroid-dependent minimal-change nephrotic syndrome, *N/E* superimposed glomerulopathy residuals were not evaluated due to overlap with the renal findings of original glomerulopathies

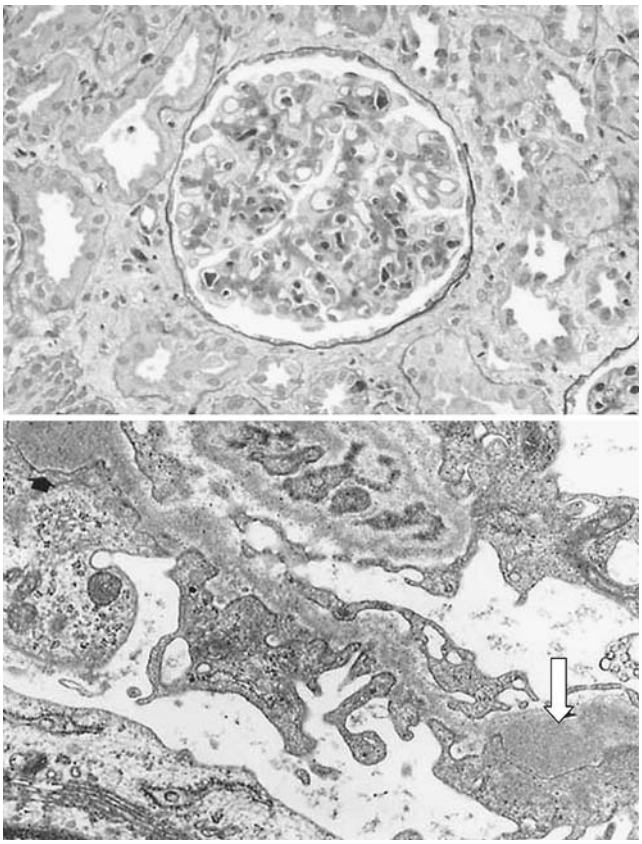

Fig. 1 The renal pathologic findings of Case 1 (Alport syndrome+ poststreptococcal glomerulonephritis). Light microscopic examination revealed mesangial and endothelial cell proliferation and neutrophils in the capillary lumen (*top panel*, PAS stain, ×400), and electron microscopic examination revealed typical glomerular basement membrane changes of Alport syndrome and a subepithelial hump (*white arrow*, *bottom panel*, ×8,000)

sonography was normal. Four weeks on oral prednisolone (2 mg kg^{-1} day^{-1}) resulted in normalization of serum albumin (3.6 g/dL) with a partial improvement in proteinuria (0.7 g/day). Her mother had persistent microscopic hematuria. A renal biopsy revealed mesangial IgA deposition, GBM changes typical of Alport syndrome, and segmental loss of type IV collagen α5 chain expression in the GBM (Fig. 2). She was then treated with enalapril (0.15 mg kg^{-1} day^{-1}), and serial urinalyses revealed persisting microscopic hematuria with minimal or no proteinuria after 6 months.

Case 5 (IgA nephropathy+PIGN) A 6-year-old boy was found to have persistent microscopic hematuria during annual school urinalysis screening. One year later, he experienced sudden-onset gross hematuria, generalized edema, and hypertension without a preceding upper respiratory tract infection. Serum creatinine was 1.1 mg/dL, serum albumin 2.0 g/dL, ASO titer was positive, and serum C3 and C4 were 41 and 16 mg/dL. A kidney biopsy revealed typical subepithelial humps and IgA mesangial and paramesangial deposition (Fig. 3). His edema, hypertension and all abnormal laboratory findings except microscopic hematuria disappeared within 1 month on conservative management only.

Case 6 (IgA nephropathy+postinfectious rapidly progressive glomerulonephritis) A 9-year-old boy developed sudden-onset gross hematuria, hypertension and generalized edema 2 weeks after an upper respiratory tract infection. He had persistent microscopic hematuria without proteinuria,

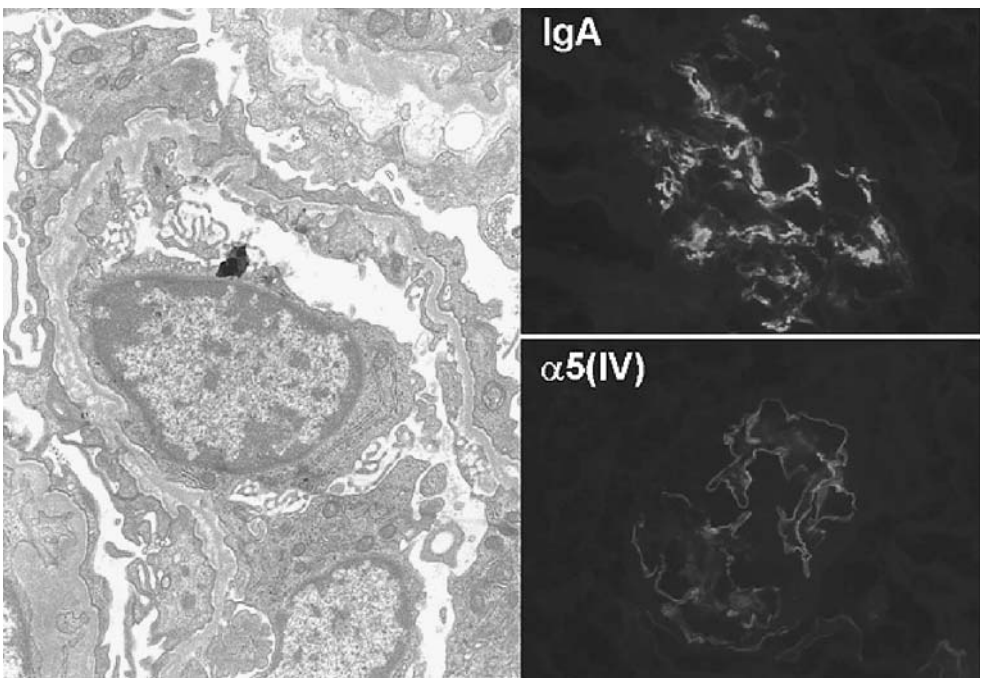

Fig. 2 The renal pathologic findings of Case 4 (Alport syndrome+IgA nephropathy). Electron microscopic examination revealed irregularly thickened and lamellated glomerular basement membranes (GBM) (*left panel*, ×8,000), and immunofluorescent microscopic examination revealed mesangial IgA deposition (*right upper panel*, ×200) and loss of type IV collagen α5 chain [α5(IV)] expression (segmental loss along the GBM and total loss along the Bowman's capsule) (*right lower panel*, ×200)

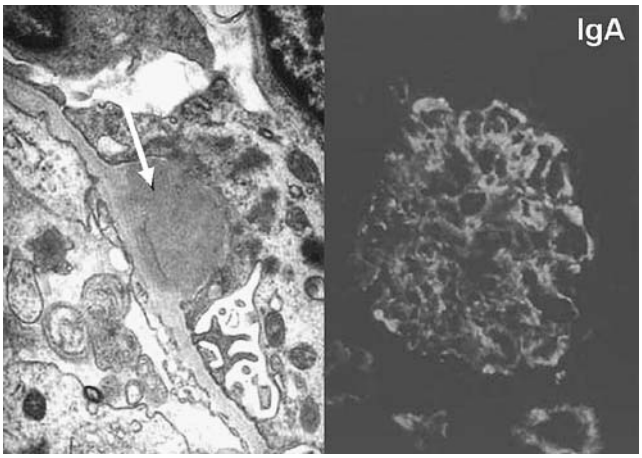

Fig. 3 The renal pathologic findings of Case 5 (IgA nephropathy+ postinfectious glomerulonephritis). Electron (*left panel*, ×5,000) and immunofluorescent (*right panel*, ×200) microscopic examinations revealed a subepithelial hump and mesangial IgA deposition, respectively

as determined during annual school urinalysis screening, of 2 years duration. Blood urea nitrogen and serum creatinine were elevated to 80 and 2.4 mg/dL, respectively. Serum albumin was 2.7 g/dL, IgA 149 mg/dL, and C3 and C4 were 28 and 19 mg/dL, respectively. Urinary protein excretion was 3.6 g/day. All serologic tests were negative.

A renal biopsy revealed cellular or fibrocellular crescents in 85% of glomeruli, typical subepithelial humps with mesangial and intramembranous electron-dense deposits, and mesangial and peripheral deposition of IgA, IgG and C3. The patient was treated with methylprednisolone pulse therapy followed by oral steroids for 1 year, cyclophosphamide for 3 months, and enalapril for 4 years until now. Last available laboratory test results at age 13 years revealed normal serum creatinine, persistent microscopic hematuria, and (1+) to (2+) albuminuria. His younger sister also had microscopic hematuria with intermittent proteinuria from the age of 5 years, and a renal biopsy, performed at age 7 years, revealed grade II IgA nephropathy.

Case 7 (minimal-change nephritic syndrome+ Henoch-Schönlein nephritis) A 3-year-old boy developed steroid-dependent nephrotic syndrome. The pathologic diagnosis after an initial renal biopsy, performed at age 4 years after the third recurrence, was of a minimal-change lesion (Fig. 4, upper panels). Moreover, follow-up urinalysis never revealed hematuria. At age 11 years when he was under the treatment with oral prednisolone every other day (1 mg kg^{-1} day^{-1}), he developed purpura on both lower extremities followed by gross hematuria, oliguria and proteinuria aggravation. Thus a second renal biopsy was done, and this revealed segmental mesangial cell proliferation and IgA deposition in the mesangium (Fig. 4, lower panels). His acute nephritic symptoms improved gradually, but steroid-dependent nephrotic syndrome and microscopic hematuria persisted.

Case 8 (Frasier syndrome+ Henoch-Schönlein nephritis) A 6-year-old girl was found to have isolated nephrotic-range proteinuria during annual school urinalysis screening, and did not respond to oral steroid and cyclosporine treatment. The first renal biopsy, which was performed at a local hospital, revealed focal segmental glomerulosclerosis involving 12% of glomeruli. At age 10 years, she developed a

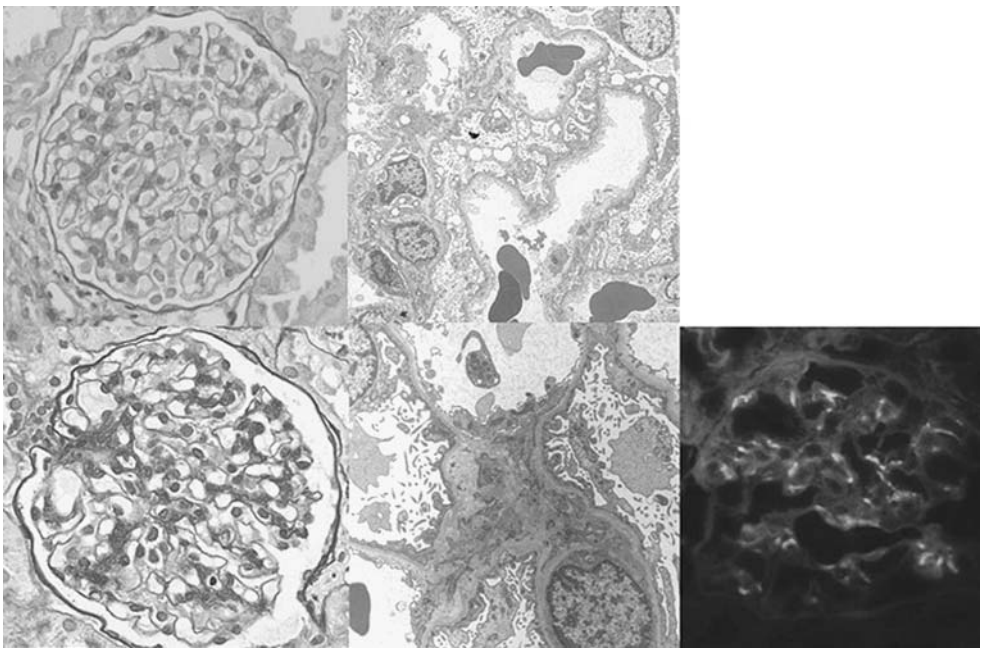

Fig. 4 The renal pathologic findings of Case 7 (minimal-change nephrotic syndrome+ Henoch-Schönlein nephritis). The first biopsy performed at age 4 years revealed a normal-looking glomerulus (light microscope, *upper left panel*, PAS stain, ×400) and wide foot process effacement (electron microscope, *upper middle panel*, ×2,500). The second biopsy performed at age 11 years revealed segmental mesangial cell proliferation (light microscope, *lower left panel*, PAS stain, ×400), mesangial electron-dense deposits and widely effaced foot processes (electron microscope, *lower middle panel*, ×4,000), and mesangial IgA deposition (immunofluorescent microscope, *lower right panel*, ×400)

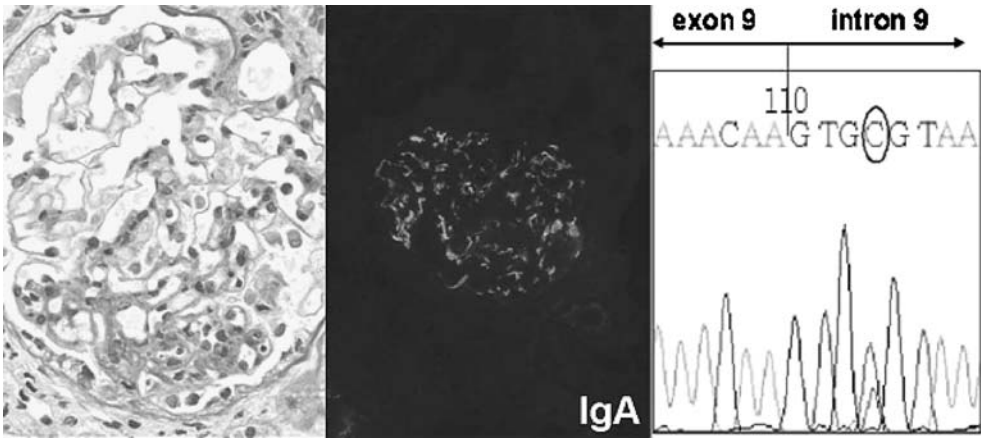

Fig. 5 Light (*left panel*, PAS stain, ×400) and immunofluorescent (*middle panel*, ×200) microscopic findings and *WT1* gene sequencing data (*right panel*) of Case 8 (Frasier syndrome+Henoch-Schönlein nephritis), showing segmental sclerosis, mesangial IgA deposition, and a heterozygous mutation of IV9+4C>T

typical skin lesion of Henoch-Schönlein purpura with gross hematuria. Her serum albumin had reduced to 2.4 g/dL, and she was transferred to our hospital. Abdominal ultrasonography failed to visualize the uterus and both ovaries despite normal female external genitalia. Her karyotype was 46,XY, and an IVS9+4C>T heterozygous mutation was detected in the *WT1* gene. A second renal biopsy revealed segmental sclerosis in 16% of glomeruli, global sclerosis in 19% of glomeruli, and crescents in 6% of glomeruli as well as mesangial IgA deposition (Fig. 5).

Case 9 (TBMN+IgA nephropathy) This male patient had gross hematuria at 1 year of age, followed by persistent microscopic hematuria. Several family members on the paternal side, including his father, had persistent microscopic hematuria with intermittent gross hematuria. His mother also had intermittent microscopic hematuria. At age 6 years, recurrent synpharyngitic gross hematuria developed, and a renal biopsy revealed grade I IgA nephropathy and diffuse GBM thinning (Fig. 6).

Discussion

A small number of papers are available that address double glomerulopathy or superimposition of a second glomerulopathy onto an original glomerulopathy. However, the majority of these papers are case reports involving a single patient or a small number of patients. This is the first systematic study reviewing the pattern and the incidence of double glomerulopathy in pediatric patients.

It is debatable whether double glomerulopathy involves the concomitant occurrence of two apparently unrelated glomerulopathies by coincidence, or whether it constitutes a separate disease entity. In our study, all cases had original glomerulopathies with a chronic long-standing course, such as Alport syndrome, IgA nephropathy, relapsing minimal-change nephrotic syndrome, steroid-resistant focal segmental glomerulosclerosis of Frasier syndrome, or TBMN. The superimposed glomerulopathies were common diseases in children, such as PSGN or PIGN, IgA nephropathy, or Henoch-Schönlein nephritis. Although the coexistence of two glomerulopathies was confirmed by a single renal

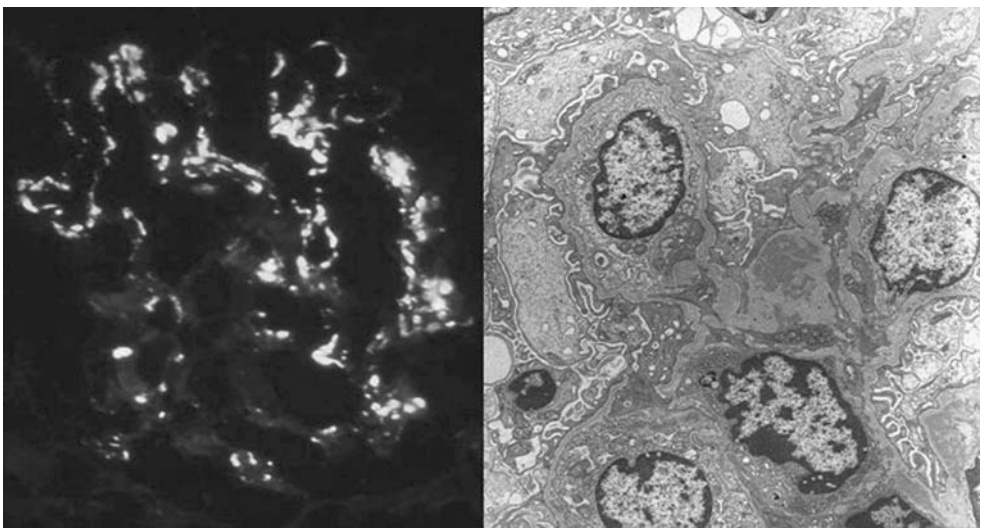

Fig. 6 The renal pathologic findings of Case 9 (thin glomerular basement membrane disease+IgA nephropathy). Immunofluorescent (*left panel*, ×400) and electron (*right panel*, ×5,000) microscopic findings revealed mesangial IgA deposition and mesangial electron-dense deposits with diffuse thinning of the glomerular basement membrane (100–130 nm in thickness)

biopsy in seven of our nine patients, preceding renal symptoms of original diseases were obtained by history taking. Thus, we consider that the patterns shown by all nine of our cases indicate the chance occurrence of two different glomerulopathies without common pathogenesis.

The incidence of double glomerulopathies found in our study was relatively high (3.1%). Monga et al. found 20 (1.2%) cases of various glomerulopathies superimposed on diabetic glomerulosclerosis [1] and 9 (0.5%) nondiabetic cases of double glomerulopathy among 1,715 adult patients, whereas Bertani et al. [2] reported 7% incidence in both diabetic and nondiabetic adults. The glomerulopathies detected in this present study were easily diagnosed and had typical clinical features (PSGN and Henoch-Schönlein nephritis), a positive family history (Alport syndrome and TBMN), or characteristic pathologic findings (IgA nephropathy, Alport syndrome, and TBMN). Thus, if we missed difficult-to-diagnose cases, the actual incidence of double glomerulopathies would be higher.

IgA nephropathy is a common disease of double glomerulopathy either as original or superimposed disease, and four patients (44%) in the present study had IgA nephropathy as a component of double glomerulopathy. Several reports have concerned IgA nephropathy superimposed by PSGN or PIGN [3–9]. The incidences of IgA nephropathy and PSGN/PIGN are relatively high, but no relationship between their pathogenesis is known. Thus these combinations suggest the coincidental occurrence of a preexisting chronic original glomerulopathy (IgA nephropathy) superimposed by a second glomerulopathy of acute onset (PSGN/PIGN). The coexistence of IgA nephropathy and other glomerulopathies, such as membranous nephropathy [10–13] or ANCA-associated crescentic glomerulonephritis [14, 15] has also been reported.

Anti-GBM nephritis superimposed on membranous nephropathy is another common double glomerulopathy combination [16–23]. For this combination, one could speculate that subepithelial immune deposits in membranous nephropathy might alter the GBM and cause release of normal or altered endogenous GBM components into the circulation, and the resultant formation of anti-GBM antibodies. However, the precise mechanism of this transformation of membranous nephropathy into anti-GBM nephritis is obscure. Membranous nephropathy is a rare disease in children, and children with this double glomerulopathy have been reported only rarely [24, 25]. Several other papers have described the coexistence of membranous nephropathy and ANCA-positive crescentic glomerulonephritis or poststreptococcal crescentic glomerulonephritis [26, 27]. In the present study, no patient had membranous nephropathy.

Bertani et al. [2] focused on the high prevalence of focal membranous nephropathy in superimposed diseases [2, 28–30], and suggested that preexisting glomerular alterations might favor an immune reaction in the subepithelial space.

PSGN or PIGN is one of the common glomerulopathies superimposed on various types of original glomerular diseases, including IgA nephropathy [3–9], membranous nephropathy [27], and focal segmental glomerulosclerosis [31]. In the present study, five patients (56%) had PSGN or PIGN as a superimposed glomerulopathy.

Non-immune-complex-mediated glomerulopathies, such as minimal-change nephrotic syndrome or focal segmental glomerulosclerosis, can also be superimposed by other glomerulopathies as in Cases 7 and 8 of the present study [1, 31].

TBMN is the most common cause of persistent glomerular hematuria in children and adults, and occurs in at least 1% of the population [32]. Interestingly, TBMN commonly occurs with various other glomerulopathies, and the incidence of this co-occurrence has been reported to be up to 75% [33, 34]. However, these findings should be interpreted with caution, as most patients with TBMN have only persistent microscopic hematuria without significant proteinuria or renal dysfunction, and do not undergo renal biopsy. In contrast, most patients with TBMN associated with a glomerular disease that causes more severe renal manifestations do undergo renal biopsy. Thus, the incidence of TBMN associated with other glomerulopathies may be lower than reported. Norby and Cisio [35] postulated three patterns of association between TBMN with other glomerulopathies: (1) artifactual association (acquired thinning of GBM) with minimal-change nephrotic syndrome, (2) coincidental association with diabetic glomerulosclerosis, membranous nephropathy, or membranoproliferative glomerulonephritis, and (3) pathogenetic association with IgA nephropathy, focal segmental glomerulosclerosis or mesangial proliferative glomerulonephritis.

It is controversial whether a superimposed glomerulopathy affects the long-term prognosis of an original glomerular disease. In our cases, acute nephritic features of superimposed glomerulopathies, even those of postinfectious crescentic glomerulonephritis, subsided in all cases. However, in cases with persistent proteinuria and/or hematuria, we were unable to assess the adverse effect of superimposing glomerulopathies because the original glomerulopathies had the same renal phenotypes. Follow-up renal biopsies may provide answers.

In conclusion, double glomerulopathies are not rare in children and the majority may occur by chance alone. The possibility of superimposed glomerulopathy should be suspected if the clinical course of a glomerulopathy changes atypically. However, the long-term influence of a superimposed glomerulopathy on renal functional deterioration remains unclear.

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