A Case of Focal Segmental Membranoproliferative Glomerulonephritis in a 5 Years Old Girl

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= **Abstract** =

Membranoproliferative glomerulonephritis (MPGN) is a progressive primary glomerulonephritis characterized by mesangial proliferation with increased mesangial matrix, subendothelial immune deposits, mesangial interposition and a double contour feature of the glomerular basement membrane. The glomerular involvement in MPGN is usually diffuse; however, cases of focal or segmental MPGN have been reported by several authors. We report a case of focal segmental MPGN with prolonged hypocomplementemia for 3 years in a 5 years old girl. **(J Korean Soc Pediatr Nephrol 2005;9:237-244)**

Key Words : Membranoproliferative glomerulonephritis, Focal segmental lesion, Hypocomplementemia

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) has become an inclusive term to describe diffuse mesangial proliferation with glomerular capillary wall thickening due to mesangial interposition and/or capillary wall deposits occurring in patients who are commonly hypocomplementemic. Based on the characteristics of the glomerular basement membrane and the location of the capillary wall deposits, MPGN has been divided into three major and distinct types [1, 2]. Type I is characterized by subendothelial electron-dense deposits and peripheral interposition of mesangium between endothelial cells and glomerular basement membrane leading to the 'double-contour' appearance of the glomerular capillary walls at light microscopy. Type II shows distinctive laminae of electron-dense, intramembranous deposits. Type III is characterized by both subendothelial and subepithelial deposits associated with basement membrane disruption, duplication and layering of lamina densa-like material [3].

In all three types of MPGN, the glomerular lesion is usually diffuse. However, it can be focal, global or segmental, and is considered to be an early manifestation of diffuse disease [4]. Most cases of focal segmental

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MPGN (FSMPGN) has been reported and followed-up in Japanese children because of routine urinary screening in school [5]. We experienced a case of FSMPGN in a 5 years old girl with prolonged hypocomplementemia for 3 years. The clinical courses, complement profiles, glomerular morphology and immunohistology of this patient are described below.

CASE REPORT

Patient : a 5 years old girl

Chief complaints : Facial edema, periorbital swelling and gross hematuriaPast history : She was born at IUP 40 weeks by normal spontaneous delivery, and her birth weight was 3.6 kg. Her previous medical history was unremarkable. All of her family hadn't had any special problems.

Present illness : A 5 years old girl presented facial edema, periorbital swelling and gross hematuria on August 17, 2001 and was hospitalized for 7 days. Facial edema and periorbital swelling was improved but gross hematuria was sustained. So, in November 20, 2001, she was transferred to Severance hospital.

Physical examinations : Her height was 111.5 cm (50-75%) and her weight was 20 kg (75-90%). Blood pressure was 90/60 mmHg. There were no problems at physical examinations.

Laboratory findings : Laboratory evaluation on admission revealed a normal complete blood count, normal serum electrolytes concentrations, blood urea nitrogen 13 mg/dL, creatinine 0.4 mg/dL, protein 7.3 g/dL, albumin 4.5 g/dL, and cholesterol 226 mg/dL. There was no liver dysfunction, cryoglobulinemia, or M-protein. Tests for antinuclear antibody and serum rheumatoid factor were negative, but antistreptolysin-O was 391 IU/mL. Serum concentration of C3 was 72.1 mg/dL, but C4 was normal at 11.4 mg/dL. Serum concentration of IgG and IgA were 1,090 mg/dL and 135 mg/dL, respectively. The urinalysis revealed many red blood cells per high power field and proteinuria (1+) on albustix. On 24 hr urine examination, protein was 162.7 mg/day, albumin 99 mg/day, CCr 99.9 mL/min/1.73m^2.

Pathology : The biopsies were performed by the percutanoeus technique using a Tru-Cut needle. Biopsy specimens for light microscopy were fixed in phosphate-buffered 10% formalin, embedded in paraffin, sectioned at 4 μm thickness, and stained with hematoxylineosin, periodic acid-Schiff, acid fuchsin orange G (AFOG), and silver methenamine. Tissue for immunofluorescence was snap frozen, cut at 4 μm, and stained with fluorescein-conjugated antisera to human IgG, IgA, IgM, C4, C3, and fibrinogen. The portion of tissue for electron microscopy was double fixed in 3% glutaraldehyde and 2% osmium tetroxide. It was then embedded in Epon 812 resin. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined with a JEOL-1200ES2 electron microscope. One or 2 glomeruli from each specimen were examined.

1st biopsy : Pathological examination of the biopsy revealed diffuse mesangial proliferation and segmental thickening of glomerular basement membrane with a double-contour feature in 15 glomeruli (41.7%) among

36 glomeruli. AFOG stain shows tiny mesangial and subendothelial fuschinophilic deposits. Focal minimal interstitial fibrosis and tubular atrophy were noted. Blood vessels were unremarkable. Immunofluorescent microscopy revealed IgG (2+), C3 (2+), and C1q (1+) deposits in the mesangium with minor capillary wall involvement. Electronic microscopy revealed relatively well preserved glomerular architecture. The glomerular basement membrane was relatively even, but had focal tiny subendothelial electron dense deposits. Epithelial foot processes were relatively well preserved. The mesangium showed electron dense deposits without cellular proliferation. These pathological findings suggested focal segmental MPGN (Fig. 1).

2nd biopsy : Pathological examination of the biopsied specimen revealed segmental mesangial widening with proliferation of mesangial cells and increased matrix feature. The silver stain showed segmental thickening of capillary wall, and a double-contour feature in 47 glomeruli (about 56%) among 84 glomeruli. Subendothelial and mesangial fuchsinophilic deposits were frequently found on AFOG stain. The interstitium, tubules, and blood vessels were unremarkable. Immu-

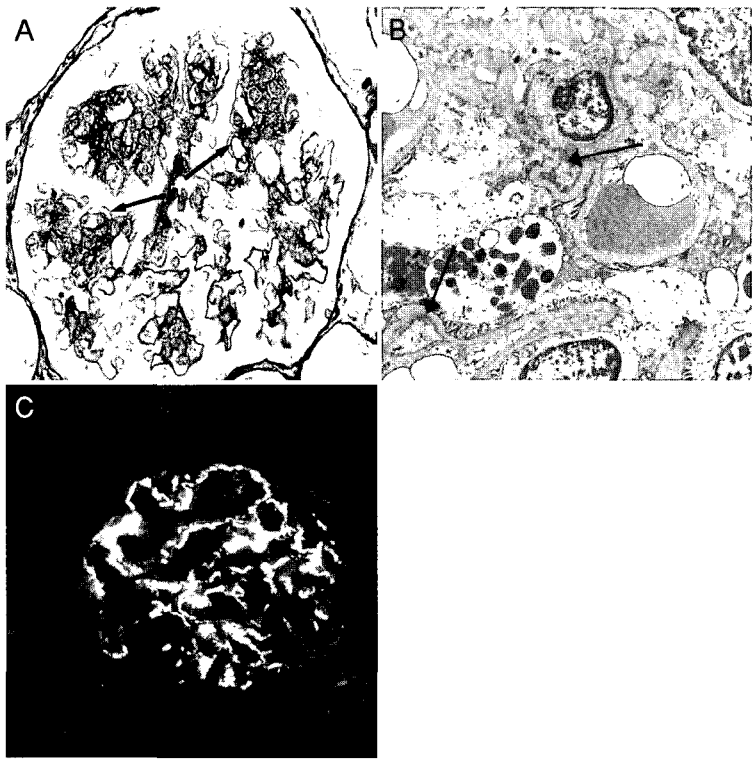

Fig. 1. First renal biopsy, December 2001. **(A)** All 28 glomeruli show diffuse mesangial proliferation and segmental double-contour feature (short bold arrow) of glomerular basement membrane. **(B)** The glomerular basement membrane demonstrated relatively even surface, but has focal tiny subendothelial electron dense deposits (large bold arrow). **(C)** The glomeruli show C3 deposits. **(A)** Methenamine-silver stain, ×400; **(B)** electron micrograph, ×2,500; **(C)** immunofluorescence microscopy, ×400.

nofluorescent microscopy revealed IgG (+), IgM (trace), C3 (2+), and fibrinogen (trace) deposits along the capillary loops with minor mesangial deposits. On electronic microscopy, the glomerular capillary loops revealed frequent subendothelial and rare intramembranous electron dense deposits with mesangial interposition. The mesangium showed electron dense deposits without proliferation of mesangial cells. The visceral epithelial cells revealed focal effacement of foot processes. These pathological findings suggested MPGN, type I (Fig. 2).

Progression and treatment : In November 20, 2001, she was transferred to Severance hospital. She was treated with conservative management. Percutaneous renal biopsy was performed on December 28, 2001 due to persistent urinary abnormality, and hypocomplementemia. She didn't have any other problem except hematuria (5-10 red blood cells per high power field) at discharge. From December, 2001 to February, 2005, this patient has been followed up in Myong-Ji hospital of Kwandong University, and microscopic hematuria, proteinuria, and hypocomplementemia were persisted (Fig. 3). We performed a second renal biopsy on February 23, 2005,

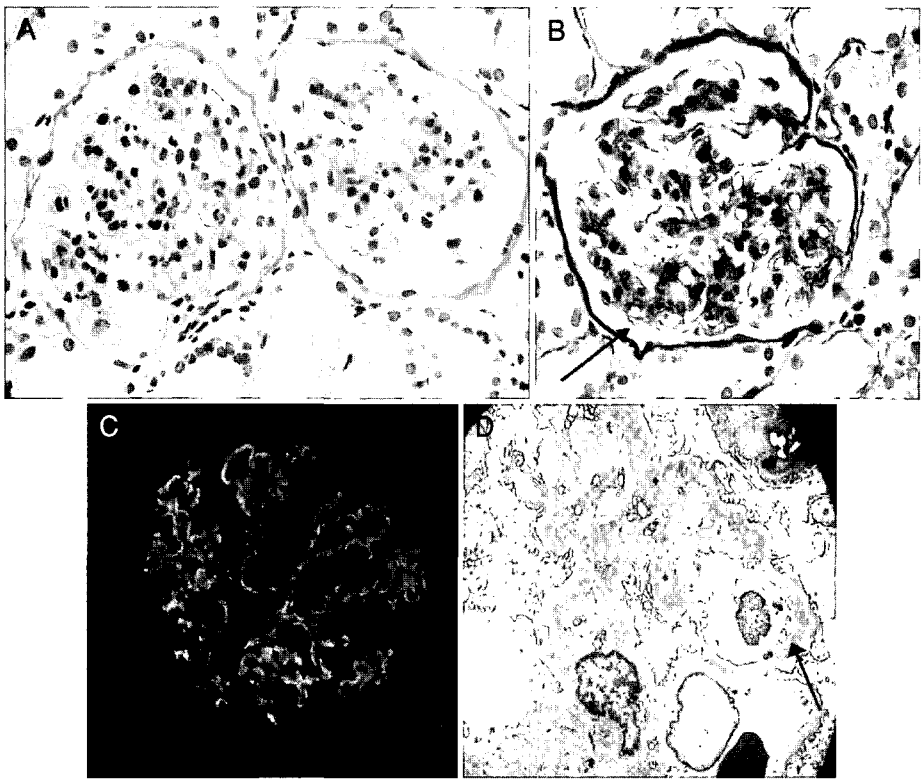

Fig. 2. Second renal biopsy, February 2005. **(A)** The lesions of membranoproliferative glomerulonephritis shown in the left glomerulus. **(B)** The silver stain show segmental double-contoured glomerular basement membrane (short bold arrow) **(C)** The glomeruli show C3 deposits. **(D)** The capillary loops reveal frequent subendothelial deposits (large bold arrow) and mesangial deposits. **(A)** Periodic acid-Schiff stain (PAS), ×400; **(B)** methenamine-silver stain, ×400; **(C)** immunofluorescence microscopy, ×400; **(D)** electron micrograph, ×2,500.

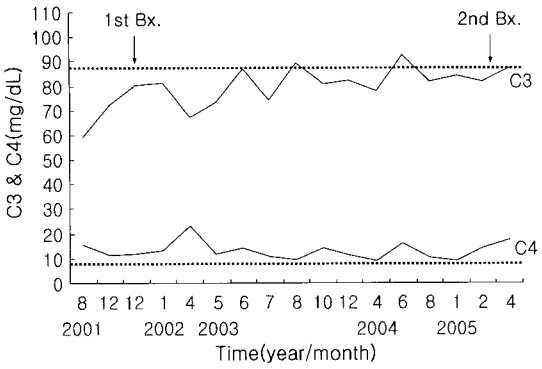

Fig. 3. The change of complement level over time. Hypocomplementemia has been prolonged for 3 years.

when she was 9 years and 1 months old. Recently, she was still hypocomplementemic with microscopic hematuria and proteinuria, but no symptoms were present. Serum concentration of C3 was 85.5 mg/dL, and C4 was normal at 12.8 mg/dL. The urinalysis revealed 5-10 red blood cells per high power field and proteinuria (1+) on albustix. Blood urea nitrogen were 10 mg/dL, creatinine 0.6 mg/dL, protein 7.5 g/dL, albumin 4.6 g/dL, and cholesterol 261 mg/dL.

DISCUSSION

Focal MPGN has not yet been established as a clinicopathological entity [3, 6-8]. Clinical findings at onset were proteinuria, microscopic hematuria, and gross hematuria [3]. In our case, she had persistent proteinuria and gross hematuria. The segmental form of MPGN has been noted by others. In 1973, Habib [1] listed four patients with focal MPGN, among 782 with biopsy evidence of glomerulonephritis, and subsequently, with her colleagues, has mentioned this form in a number of reports of the same patient population. Focal segmental MPGN (FSMPGN) has been defined by researchers as a condition with focal segmental lesions in up to 33% [3], 50% [8], and 80% [9] of glomeruli. Focal MPGN may progress to typical MPGN, acute glomerulonephritis (AGN) may progress to focal MPGN, and typical MPGN may regress to focal MPGN [8]. Therefore focal MPGN is considered to be an early type of typical MPGN or a stage in the cure of typical MPGN [5].

In type I and type II MPGN, the characteristic lesion is diffuse involvement to all glomeruli and tufts equally. In type III, the extent of the alteration of the capillaries within a glomerulus may be non-uniform, giving a somewhat focal appearance to the lesion [3]. In the patient in the present report, however, the contrast between uninvolved glomeruli and tufts and the segmental lesion was much more striking than that could be typically seen in type III. Although all glomeruli showed some degree of proliferation, the one seen in the segmental lesion was far more intense.

In our case, the diagnosis of first renal biopsy was FSMPGN, and of second renal biopsy was MPGN, type I. Strife et al. [3] suggested that the segmental MPGN lesion appears to be an early manifestation of, most commonly, Type I, and less commonly, Type III. Evidence that the disease is in an early stage at presentation is the youth of the patients and the absence of marked clinical and laboratory abnormalities. In their study, only one patient had hypoalbuminemia, and none had hypertension or azotemia. In our case, there weren't hypoalbuminemia, hypertension,

and azotemia. One presented with only microscopic hematuria without proteinuria and the disease was suspected because of lower C3 level. In their study, however, no progression of disease was observed suggesting that segmental MPGN is usually mild as well as an early form of disease. The disease in all patients has been improved as diagnosed by the recovery of complement level to normal and by improvement of the results in urinalysis and in glomerular morphology on subsequent biopsies. Iitaka et al. [4] presented that the follow-up biopsies of FSMPGN showed global sclerosis, but no interstitial changes or crescents were observed. These findings suggest that FSMPGN is mild form of disease. Yoshikawa et al. [9] presented that the absence of marked clinical and laboratory abnormalities suggested that the severity of focal MPGN is mild.

According to the experience of others, this disease is relatively benign as well. Watson et al. [7] reported 33 patients with type I MPGN and subtyped these patients into three groups; 9 patients with FSMPGN, 18 with diffuse global MPGN, and 6 with mixed segmental and global MPGN. Of the FSMPGN group, 8 (89%) demonstrated no evidence of renal insufficiency. In contrast, 11 (61%) of the diffuse global MPGN group and 4 (67%) of the mixed group developed into chronic or end-stage renal failure. Therefore, that FSMPGN could be a good predictor of a favorable clinical outcome. Biopsy results of FSMPGN did not demonstrate sclerosed or crescentic glomeruli. IF microscopy showed granular deposits of IgG, IgM, and C3 along the capillary walls of glomeruli like the findings of our two renal biopsies (Fig. 1C, 2C). Subendothelial deposits and double contouring of glomerular capillary basement membranes and mesangial interposition were seen by EM in all FSMPGN patients like the findings of our two renal biopsies (Fig. 1B, 2D). Kincaid-Smith [10] showed that a focal and segmental proliferative glomerulonephritis progressed into a diffuse MPGN over a 5 years period. This observation supports the concept that focal and segmental MPGN represents an early form of disease.

Focal double contour of the glomerular capillary wall is occasionally found in a variety of glomerulopathies such as IgA nephropathy [11], Henoch-Schönlein nephritis [12], focal segmental glomerulosclerosis [13], etc. However, they do not have diffuse deposition of C3 along the glomerular capillary walls with lobular pattern [9]. Yoshikawa et al. [9] reported that deposition of C3 was observed in all patients with focal as well as diffuse type I MPGN. Deposition of C3 along the glomerular capillary walls in all patients with type I MPGN has been reported previously [14, 15]. Yoshikawa et al. [9] suggested that diffuse granular deposits of C3 along the capillary walls with a lobular distribution are confined to type I MPGN and lupus nephritis and seen in all patients with type I MPGN. These deposits, therefore, constitute the most reliable distinction between type I MPGN, particularly FSMPGN and other glomerulopathies. Deposition of C3 along the capillary walls was diffuse and global in all patients with FSMPGN. If C3 deposition is responsible for the development of double-contour change, it is possible that a focal

MPGN progresses to diffuse MPGN. Strife et al. [3] also demonstrated global C3 deposition in all glomeruli of all patients with FSMPGN. In our two biopsies, there were C3 deposits along the capillary loops with minor mesangial deposits (Fig. 1C, 2C).

The treatment for focal MPGN is yet to be established. Prednisolone, which was used in most published studies [3, 16], gives FSMPGN an excellent prognosis. Moorhead [17] noted that the persistent hyperlipidemia observed in nephritic syndrome is associated with the progression of renal disease. Consequently lipid-lowering therapy is now prescribed for patients with nephrotic syndrome [18]. We treated our patient with simvastatin, a lipid-lowering drug, when she developed hypercholesterolemia. Kano et al. [5] suggested that repeated renal biopsies should be performed at the recrudescence of urinary or blood findings, and serum total protein, albumin, C3, C4, CH50, BUN, creatinine, and urinalysis should be checked at regular intervals. They reported a girl with type I MPGN diagnosed by the third renal biopsy for 3 years. They performed repeated renal biopsy because of microscopic hematuria, proteinuria, and the low serum complement level, and suggested that it is necessary to continue the careful observation of the patient for an extended period, and a fourth renal biopsy will be performed in the future.

Strife et al. [3] also treated their patients with FSMPGN using alternate-day (ALD) prednisone therapy. But, growth could potentially be stunted by ADL prednisolone treatment [19]. The growth and duration should be observed carefully, so that ALD prednisolone could be tapered off afterwards, especially in those patients with hematuria and segmental lesions of MPGN, since patients with FSMPGN seem to have an excellent prognosis [4].

In summary, we experienced a case of FSMPGN with continuous hypocomplementemia for 3 years in 5 years old girl patient. The results of two renal biopsies demonstrated FSMPGN, and MPGN type I.

In conclusion, focal segmental MPGN is a mild form of MPGN, which may present with acute nephritic syndrome and hypocomplementemia. Although the patient was asymptomatic, the patient should be followed since histological progression may occur.

한 글 요 약

5세 여아에서 발견된 초점분절 막증식사구체신염 1례

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막증식사구체신염은 혈관사이바탕질, 내피밑층의 면역침착물의 증가와 사구체 기저막의 이중윤곽을 특징으로 하는 증식성 일차성 사구체신염이다. 막증식사구체신염에서의 사구체 침범은 주로 미만성이지만, 초점성 또는 분절성의 막증식사구체신염이 몇몇 발표되었다. 그러나, 우리나라에서는 아직 발표된 예가 없어서 이에 저자들은 5세 여아에서 3년 동안 저보체혈증 및 현미경적 혈뇨와 단백뇨를 보인 초점분절 막증식사구체신염 1례를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.

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