J Tokyo Wom Med Univ
79 (5・6) 224～227 (2009)

Report

A Case of Focal Segmental Glomerulosclerosis Showing Morphological Change from the Not Otherwise Specified (NOS) to the Collapsing Variant

Takahito MORIYAMA, Mitsuyo ITABASHI, Takashi TAKEI, Keiko UCHIDA, Kazuho HONDA* and **Kosaku NITTA**

Department of Medicine IV, Tokyo Women's Medical University
*Department of Pathology II, Tokyo Women's Medical University

(Accepted Apr. 9, 2009)

We describe a unique case of focal segmental glomerulosclerosis (FSGS) with morphological change from not otherwise specified (NOS) to collapsing variant. A 28 years old woman, who was diagnosed to have the NOS of FSGS at the age of 17 years, was admitted to our hospital. A diagnosis of nephrotic syndrome and moderate renal dysfunction was made based on her clinical and laboratory data. Renal biopsy was performed and the histological findings were consistent with the collapsing variant of FSGS, which was different from the results of the first biopsy. The collapsing variant of FSGS has been reported to be strongly associated with human immunodeficiency virus (HIV) nephropathy and the black race. However, it has recently been reported in association with idiopathic FSGS and also in Caucasians, but still uncommon in Asian. Therefore, this variant is seemed to be very rare case in Japan, and morphological change from the NOS to the collapsing variant is also seemed to be uncommon.

Key words: collapsing variant, not otherwise specified, morphological change, focal segmental glomerulonephritis

Introduction

Idiopathic focal segmental glomerulosclerosis (FSGS) is classified into five different variants based on the pathological findings, namely, the cellular variant, collapsing variant, tip variant, perihilar variant, and not otherwise specified (NOS) (the Columbia classification)[1]. The collapsing variant is characterized histopathologically by global and segmental glomerular capillary tuft collapse and podocyte hypertrophy and hyperplasia[2], and clinically by heavy proteinuria, a high incidence of nephrotic syndrome, a high serum creatinine level, rapid progression, resistance to steroid therapy, and a poor prognosis in terms of the renal survival[1)2)]. Recently, the prevalence of this variant has been reported to be increasing[1)2)], however, there are few reports until date of adult onset of this variant from Japan. We report the rare case of morphological change from the NOS to the collapsing variant of FSGS, which also seems to be the uncommon case of the adult-onset collapsing variant of FSGS reported from Japan.

Case Repoot

The patient was a 28 years old Japanese woman who referred to our department with a history of generalized fatigue. She had previously been observed at the pediatrics division of our Kidney Center after accidental detection of proteinuria when she was 15 years old. At that time, her laboratory findings were as follows: serum total protein, 6.8 g/dl; albumin, 4.3 g/dl; serum creatinine, 0.51 mg/dl, total cholesterol, 183 mg/dl. Urinalysis was negative for red blood cells, the urinary protein excretion was 0.38 g/day, and the creatinine clearance was 94.9 ml/min. There was no evidence of hypertension, obesity, collagen disease, diabetes or other systemic diseases, and abdominal ultrasonography and intravenous pyelography revealed no abnormalities of the kidney or urinary tract. Renal biopsy was performed at 17 years old. Out of 42 glomeruli, only three showed segmental glomerulosclerosis with glomerular tuft adhesion and periglomerular fibrosis (Fig. 1A, B). The other glomeruli did not show

mesangial changes, stalk thickening or epithelial reaction. Mild tubular atrophy and interstitial fibrosis were observed (5-10%) in the cortical area and there was no evidence of arteriolar sclerosis. A diagnosis with NOS variant of FSGS was made because there were no findings of the other variant in the 42 consecutive sections, and the patient was initiated on treatment with lisinopril hydrate at 5 mg/day and dilazep hydrochloride at 300 mg/day for her mild proteinuria. As her follow-up visits were irregular and compliance with medication was poor, her urinary protein excretion did not decrease and renal function gradually worsened. The serum creatinine was 0.77 mg/dl and the urinary protein excretion was over 1.0 g/day, when the patient was 24 years old. By the time the patient became 25 years old, her urinary protein excretion increased to 2.3 g/day, however, she discontinued her visits to our hospital thereafter.

Three years later, when she was 28 years old, the patient visited to our hospital again suffering from general fatigue. Her laboratory data were consistent with nephrotic syndrome, her serum total protein was 5.4 g/dl, serum albumin was 2.9 g/dl, serum total cholesterol was 368 mg/dl, and urinary protein excretion was 4.3 g/day. Her renal functions were also worse, with the serum creatinine concentration increased to 1.56 mg/dl and the creatinine clearance decreased to 44.9 ml/min. Renal biopsy was performed immediately. Out of 23 glomeruli examined, three showed global sclerosis and there was no crescent formation. Nine glomeruli showed glomerular capillary tuft collapse, capillary wall thickening, and hypertrophy and hyperplasia of the podocytes and foam cells in 42 consecutive sections (Fig. 2A, B). Moderate tubular atrophy and interstitial fibrosis were noted (30%) in the cortical area, and foam cells were found in the proximal tubules. There was no evidence of arterial or arteriolar sclerosis. Immunofluorescent study showed mesangial deposition of IgM, IgA and C3. The serum antibody for human immunodeficiency virus (HIV) was negative and she had never received pamidronate or other bisphosphonates, therefore she was diagnosed with idiopathic FSGS-collapsing variant and

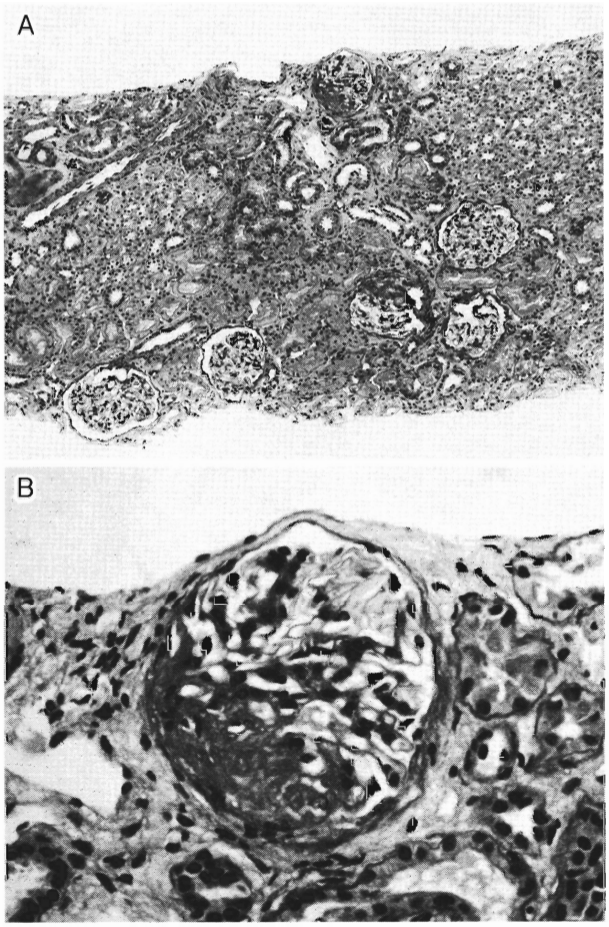

Fig. 1 Light-microscopic findings at the first renal biopsy
A: Lower magnification (PAS stain, ×20) shows 2 glomeruli with perihilar sclerosis among 6 glomeruli, mild tubular atrophy and interstitial fibrosis, and interstitial inflammatory cells infiltration around glomeruli with segmental sclerosis; there is no evidence of arterial or arteriolar sclerosis.
B: Higher magnification (PAS stain, ×66) shows segmental sclerosis with glomerular tuft adhesion. Hyalinosis and foam cells are not seen in the sclerotic lesion, and podocyte hypertrophy and hyperplasia are not noted in this glomerulus.

started treatment with prednisolone at 0.8 mg/kg/day after steroid semi-pulse therapy, mycophenolate mofetil at 1,000 mg/day, losartan at 25 mg/day, eplerenone at 25 mg/day, lovastatin at 40 mg, and aspirin at 100 mg/day. However two months after therapy, her laboratory data were still consistent with nephrotic syndrome, the urinary protein excretion was 3.73 g/day.

Discussion

After reporting the Columbia classification, the characteristic clinical and histological findings and

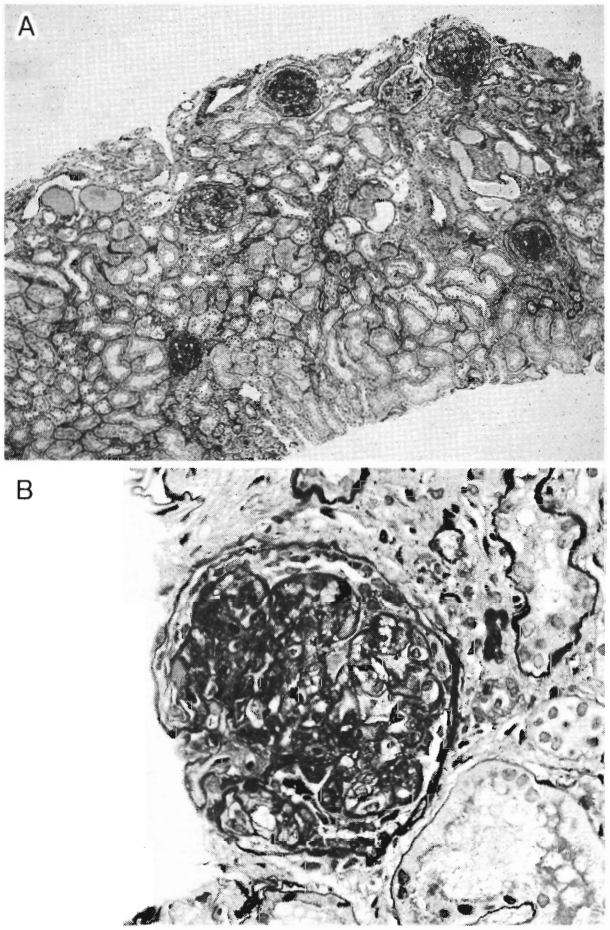

Fig. 2 Light microscopic findings at the second renal biopsy
A: Lower magnification (PAS stain, ×20) shows 4 glomeruli with collapse of the capillary lumen, 1 glomerulus with global sclerosis among 6 glomeruli, tubular and interstitial changes around the collapsing glomeruli; there is no evidence of arterial or arteriolar sclerosis.
B: Higher magnification (PAS stain, ×66) shows global narrowing of the capillary lumen with thickening of the capillary wall, hypertrophy and hyperplasia of the podocytes and foam cells.

the prognosis of each variant have been examined. Chun et al reported 87 cases of FSGS in the United States[3]. They categorized these cases on the basis of histologic criteria into those with a classic scar (41.4%), the cellular and collapsing lesion (45.9%), and the tip lesion (12.6%), and reported that the cellular and collapsing lesion was characterized by severe proteinuria, was most frequent in the black race (73%), and was associated with the worst renal survival at 10 years in non-remission cases (21%). Thomas et al also reported 197 cases of FSGS in the United States[4]. They divided the cases according to the histological findings into the cellular variant (3%), tip variant (17%), perihilar variant (26%), collapsing variant (11%), and NOS (42%). They reported that the collapsing variant affected younger and, more often, black patients (91%), and was associated with a worse renal survival as compared to the other variants (1 year, 74%, and 3 years, 33%). Deegens et al reported 93 cases of FSGS from the Netherlands[5]. They reported the frequencies of each variant as follows; NOS, 32%; tip variant, 37%; perihilar variant, 26%; collapsing variants, 5% and celular variants, 0%. All of their patients were native Dutch and there were no African-American patients; they also showed that the collapsing variant of all the variants was associated with the worst 5 years renal survival rate (30%) (NOS 63%, tip 78%, and perihilar 55%). According to these reports, the collapsing variant occurs most frequently in the black race and is associated with the worst renal survival rate among the variants. To the best of our knowledge, there are few case reports of an adult with the collapsing variant of FSGS from Japan, and moreover there are no reports of the collapsing variant in any other Asian populations. Considering that the frequency of the collapsing variant in the European population is only 5%, the occurrence of the collapsing variant of FSGS appears to be associated with the racial background and it seemed to occur very rarely in Asia.

Our case is also the rare case of the collapsing variant in which the morphological change from NOS. The patient had discontinued her visits to the hospital and had not received any treatments for four years. During the period while she did not visit the hospital, the morphological transition of the pathological variant might occur, and her laboratory data became consistent with the nephrotic syndrome and deteriorated renal function. Moreover, her nephrotic syndrome seemed to be resistant to steroid and immunosuppressive therapy. The histological findings at the first biopsy were consistent with the NOS of FSGS. The NOS is diagnosed by exclusion of the other variant[1]. The patient was not obese or hypertensive, and no underlying cause for the glomerular hyperfiltration could be detected.

Therefore, the diagnosis of idiopathic NOS of FSGS was made. Considering that the laboratory data at the first biopsy showed only mild abnormalities, her FSGS seemed to be in the early stage. The collapsing variant of FSGS is characterized by segmental or global collapse of the glomerular capillaries and podocyte hypertrophy and hyperplasia. The pathogenesis of the collapsing variant is visceral epithelial cell injury leading to cell cycle dysregulation and a proliferative phenotype[2]. We speculate that there are some cases that may show morphological changes of the collapsing variant, because all variants share the common features of podocyte alterations at the ultrastructural level, although the extent of the glomerular tuft collapse differs among the variants[1]. The etiology may involve many unknown factors, and a common characteristic to all variants may exist in the pathogenesis of FSGS.

In conclusion, we should pay particular attention to cases of FSGS showing the exacerbation of clinical findings during the clinical course, and repeated biopsy is very important to detect the morphological change of the pathological variant consistent with the deterioration of clinical manifestations.

References

1) **D'Agati V**: Pathologic classification of focal segmental glomerulosclerosis. Semin Nephrol **23**: 117–134, 2003
2) **Schwimmer JA, Markowitz GS, Valeri A et al**: Collapsing glomerulopathy. Semin Nephrol **23**: 209–218, 2003
3) **Chun MJ, Kobert SM, Schwartz MM et al**: Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol **15**: 2169–2177, 2004
4) **Thomas DB, Franceschini N, Hogan SL et al**: Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int **69**: 920–926, 2006
5) **Deegens JKJ, Steenbergen EJ, Borm GF et al**: Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population-epidemiology and outcome. Nephrol Dial Transplant **23**: 186–192, 2008

非特異型から虚脱型に形態変化をきたした巣状糸球体硬化症の一例

東京女子医科大学第四内科学
*東京女子医科大学第二病理学

森山（モリヤマ） 能仁（タカヒト）・板橋美津世（イタバシミツヨ）・武井 卓（タケイタカシ）
内田（ウチダ） 啓子（ケイコ）・本田（ホンダ） 一穂（カズホ）*・新田（ニッタ） 孝作（コウサク）

症例は28歳女性．15歳時に健診で初めて尿蛋白を指摘され当院腎小児科を受診した．初診時より尿蛋白0.5 g/日程度で経過していたが，17歳時に1.0 g/日まで増加し，腎生検を施行された．3/43個の糸球体に係蹄壁の癒着を伴う分節状の硬化を認め非特異型の巣状糸球体硬化症と診断された．アンギオテンシン変換酵素阻害薬，抗血小板剤を投与されたが，通院は不定期で25歳以降受診しなかった．28歳時倦怠感を自覚し当科に紹介受診となった．初診時クレアチニンは1.5 mg/dlと軽度上昇し，血清総蛋白5.4 g/dl，アルブミン2.9 g/dl，尿蛋白4.3 g/日とネフローゼ症候群を呈していた．腎生検の結果9/23個の糸球体で係蹄壁の肥厚と係蹄腔の狭小化を伴い，上皮の増生と変性，泡沫状変化を認め虚脱型の巣状糸球体硬化症と診断した．虚脱型の巣状糸球体硬化症はHIV腎症との関連が深く黒人に多いとされている．特発性の虚脱型巣状糸球体硬化症に関する報告は本邦では少なく，またその中でも本症例のように非特異型より虚脱型に変化した報告例は特に稀有と考えられる．