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A Case of Membranous Glomerulonephritis Coexisting with Focal Segmental Glomerulosclerosis

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= 국문초록 =

국소 분절 사구체 경화증을 동반한 막성 신증 1예

연세대학교 의과대학 내과학교실, 병리학교실,* 이화여자대학교 의과대학 내과학교실**
이한성 · 김동기 · 김승준 · 박선영 · 유동은 · 오형중 · 장혜정** · 정현주* · 최규헌

63세 여자 환자로 하지 부종과 거품뇨를 주소로 입원하였다. 환자는 1년전 고혈압 진단받고 약물 복용 중이었다. 입원 당시 이학적 검사상 혈압 140/90mmHg이었고, 하지 부종 이외의 이상 소견은 보이지 않았다. 혈청 생화학 검사상 혈중 요소질소 12.6mg/dL, 크레아티닌 0.6mg/dL, 총단백 5.1g/dL, 알부민 2.4g/dL, 총콜레스테롤 277mg/dL이었으며 기타 면역혈청 검사, 바이러스성 간염 표지자 등은 모두 음성이었다. 24시간 소변 검사상 단백질 그리고 알부민이 각각 2,325mg, 1,772mg 배출되었다. 복부 초음파 검사에서는 특이 소견 보이지 않았다. 신생검 시행 하였으며 막성 신증(Churg's 제 2 기)과 국소 분절 사구체 경화증 소견 보여 안지오텐신 수용체 억제제와 이뇨제를 투여하였다. 이후 외래 추적 관찰 중 시행한 24시간 소변 검사상 요단백이 9,688mg까지 증가하고 부종이 조절되지 않아 재입원 후 싸이클로스포린과 스테로이드 경구 투여하였다. 이후 단백뇨 감소(24시간 소변 검사상 요단백 100mg)하고 부종 호전되어 퇴원 후 현재 외래 추적 관찰 중이다.

막성 신증은 흔히 다른 사구체 병변을 동반하는 것으로 보고 되고 있다. 특히 국소 분절 사구체 경화증은 막성 신증의 제 3 기 혹은 4기 등에 적지 않은 빈도로 발현되어 막성 신증의 이차적인 병변으로 생각되어 지기도 한다. 본 증례는 막성 신증의 초기 단계에 국소 분절 사구체 경화증이 동반되어 막성 신증의 이차성 병변이 아닌 원발성 병변이 의심되어 보고하는 바이다.

중심 단어 : 막성신증 · 국소 분절성 사구체 경화증.

Introduction

Membranous glomerulonephritis (MGN) is featured by diffuse changes in the capillary walls of the glomerulus and represents about 20% of cases of adult-onset nephritic syndrome[1]. MGN is associated with various kinds of other glomerular lesions such as IgA nephropathy[2)3)], diabetic glomerulosclerosis[4)5)], minimal change disease[5)], and focal glomerulosclerosis[6)7)], and the

association correlates closely with the clinical course of MGN[2-6].

Focal segmental glomerular sclerosis (FSGS) is characterized by the segmental sclerosis involving glomeruli in a focal distribution[8]. It is classified into idiopathic, complex and secondary types. Secondary FSGS is observed in patients with history of heroin abuse, human immunodeficiency virus infection, transplantation and tumors. The two glomerular disorders can lead to hypertension and renal failure.

FSGS is said to be observed in patients with later stages of MGN, especially Churg's stages 3 and 4, and are associated with significantly poorer prognosis than patients with MGN alone.

Although a study regarding MGN coexisting with FSGS has been reported in a foreign article[9], there has been no reported case in Korean medical literature, especially those regarding occurrence of MGN in earlier stages of FSGS. We report here a patient with early MGN and coexisting FSGS lesions.

Case Report

A 63 year-old woman presented with lower extremity edema and foamy urine with duration of two months. The patient was diagnosed of hypertension a year ago and was currently on anti-hypertensive medications (calcium channel blockers and diuretics). She denied history of diabetes mellitus and viral hepatitis. Blood pressure on admission was 140/90mmHg, pulse rate 79 beats/min, respiration rate 21/min and body temperature was 36.6℃. Physical examination failed to show any abnormalities except for pitting edema of the lower extremities. She had a BUN level of 12.6mg/dL, Cr level of 0.6mg/dL and a albumin level of 2.4g/dL. The rest of laboratory findings were as follows : Hemoglobin level 12.9g/dL, hematocrit 35.9%, white blood cell count 7,600/mm^3 with a normal differential count, platelets 290,000/mm^3, total protein 5.1g/dL, calcium 8.4mg/dL, phosphorous 3.8mg/dL, total cholesterol 277mg/dL, aspartate aminotranferase 26IU/L, alanine aminotransferase 33IU/L, uric acid 7.9 mg/dL. Serum C3 and C4 were not decreased with a level of 139.8mg/dl and 35.2mg/dL respectively.

IgG, IgA and IgM levels were also normal with levels of 1,350.7mg/dL, 322.5mg/dL and 57.3mg/dL each. Serological investigations for autoimmune disorders, such as hepatitis B surface antigen, anti hepatitis C antibody, anti human immunodeficiency virus antibody, anti-nuclear antibody, anti-double strand DNA antibody, anti-neutrophil cytoplasmic antibodies (ANCA) cryoglobulin were negative. The 24 hour urine protein was 2,325mg. No abnormal finding was noted on chest radiography. An abdominal ultrsonography revealed no abnormalities A percutaneous renal biopsy under ultrasound guidance was performed. Of the fifteen glomerulies were obtained eleven of them demonstrated minimally thickened glomerular basement membrane with spike formation on

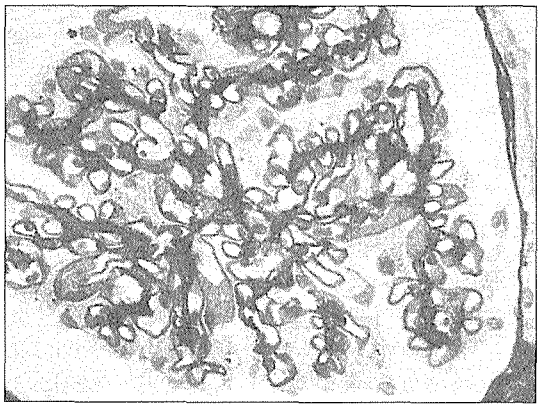

Fig. 1. A light microscopy demonstrates minimally thickened spikes on the glomerular basement membrane (arrow) (Methanamine silver stain, ×400).

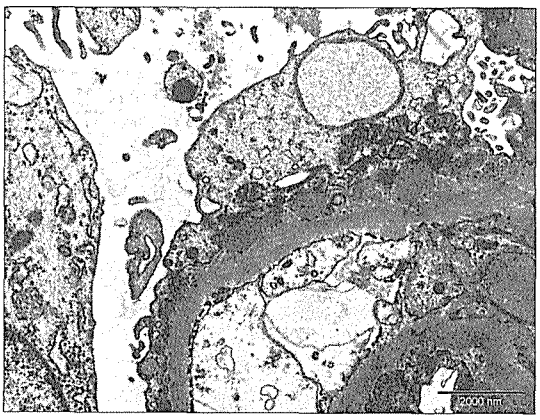

Fig. 2. Electron micrograph of a portion of glomerulus showing diffusely thickened basement membrane with subepithelial electron dense deposits (arrow). The epithelial foot processes are diffusely effaced (× 10000).

silver stain (Fig. 1). The tubules showed atrophy with mononuclear infiltration. Electron micrography showed diffusely thickened basement membrane with subepithelial electron dense deposits (Fig. 2). The specimen demonstrated granular IgG deposits along the capillary wall on immunoflourescence staining (Fig. 3). One glomerulus showed global sclerosis and one glomerulus showed segmental sclerosis at light microscopy (Fig. 4). The pathological findings were compatible with MGN (Churg's stage II) with FSGS. Treatment was started with angiotensin receptor blocker and diuretics. The patient was discharged and closely followed at the out-patient clinic.

Despite therapy, she remained edematous and continued to have proteinuria with protein of 9.69g/d. She was re-admitted and was administered cyclosporine (2 mg/kg/day) and oral prednisolone (0.5mg/kg/day). The patient responded to therapy, demonstrating decrease in proteinuria (less than 100mg/d) and edema. The patient is currently visiting the out-patient clinic on a regular basis without signs of relapse for over a year.

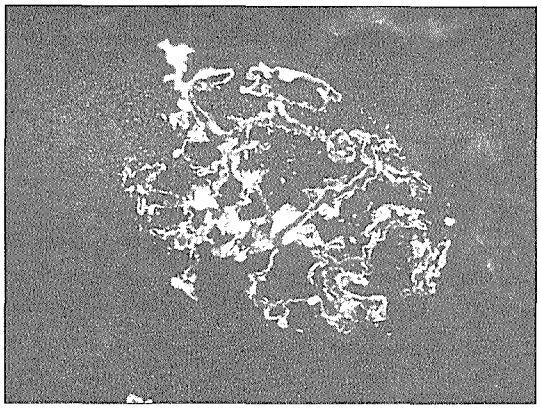

Fig. 3. Immunofluorescence microscopy reveals IgG deposits along the capillary wall.

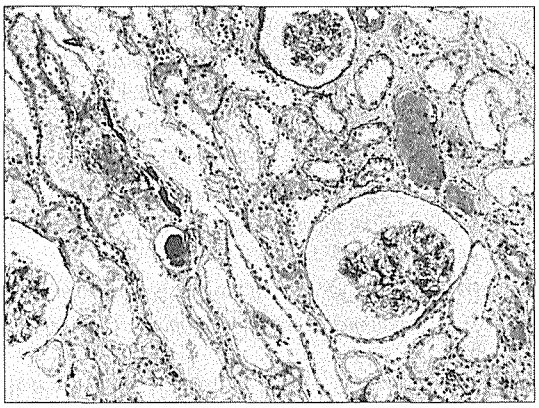

Fig. 4. Focal segmental glomerulosclerosis in membranous nephropathy. Small areas of hyalinosis are shown (PAS stain, ×150).

Discussion

Membranous glomerulonephritis and focal segmental glomerulosclerosis are important causes of the nephrotic syndrome and renal failure in adults.

Membranous glomerulonephritis is a disease with glomerular basement membrane thickening and subepithelial immune deposits. It's etiology and mechanism are not fully understood. The clinical course varies with 20 to 45% of patients developing chronic renal failure within 10 to 15 years after diagnosis, while 20% of patients experience spontaneous remission.

Focal segmental glomerulosclerosis accounts for 15–20% of nephrotic syndrome in adults[10]. The first cases were reported by Arnold Rich in 1957, when he described clinico-pathological characteristics of twenty children with nephrotic syndrome, who revealed segmental sclerosing lesions near the juxtamedullary zone of the cortex and were associated with higher rates of hypertension and uremic related deaths. The subsequent studies showed FSGS to be refractory to treatment, with few cases of spontaneous remission and frequent relapses after transplantation. FSGS accounts for upto 15% of end stage renal disease. FSGS is classified into idiopathic, complex and secondary types. The secondary type is associated with heroin abuse, HIV infection, chronic lithium exposure, obesity, recovery phase of inflammatory insult, loss of nephrons, and rarely with tumors, like lymphoma[11]. Although the pathogenesis of this disease is unclear, glomerular damage by genetical, metabolical, and environmental causes, leakage of protein into renal tubules leading to damage of tubules through reabsortion and interstitial fibrosis all seem to contribute to the pathogenesis of FSGS.

The meaning of focal segmental glomerular sclerosis superimposed on membranous glomerulonephritis is uncertain. Its mechanism is also unclear.

Few studies have been carried out to find the signi-

ficance of this coexistence, and have come up with similar results.

Ehrenreich and Churg were the first authors to publish observations of lesions of focal sclerosis in 30% of cases of membranous nephropathy, and since then, five more studies have been published and stressed the portentous meaning of such lesions.

Iwashashi[12] compared pure MGN patients with MGN combined with FSGS patients, and concluded MGN combined with FSGS patients had higher systolic blood pressure, creatinine and had longer duration of proteinuria. The stage of membranous lesions were more advanced, tubular atrophy, interstitial fibrosis and arteriosclerosis were more severe.

VanDamme et al[13] observed MGN associated with FSGS lesions and reported lower rates of remission in the combined lesion group than the pure membranous lesion one.

Wakai and Magil[14] compared factors affecting the prognosis of the disease course between the two groups and concluded patients with mixed MGN and FSGS lesions showed more severe tubulointerstitial changes and eventually progressed to end stage renal disease at a higher rate.

Lee and Koh[9] studied 41 patients with FSGS lesions who had pre-existing MGN. They had a greater degree of mesangium expansion, glomerular basement membrane thickening, interstitial fibrosis, lesions of which were correlated with higher levels of creatinine.

Dumoulin et al[15] compiled the past studies confirmed that coexisting FSGS lesions represent a particular subset of MGN. They also found as did Lee and Koh[9], that superimposed FSGS is significantly more common with advancing stages of membranous lesions.

As a whole, the membranous glomerulonephritis with focal segmental glomerulosclerosis are more advanced, nearly all in stages III and IV, suggesting that the sclerotic lesions might be due to secondary changes. But in our case, the membranous lesions were described as stage II, raising the possibility that the sclerotic lesions observed in our case result from idiopathic form of FSGS.

The studies comparing the remission rates between patients with or without lesions of FSGS superimposed on lesions of MGN show that the combined lesion were associated with lower remission rates. The combined lesions therefore lead to more complicated and hazardous therapy.

In summary, the patients with focal segmental glomerulosclerosis superimposed on membranous nephropathy tend to have a poorer prognosis than patients with membranous nephropathy. Sequent studies to verify, whether the sclerotic lesions developed due to secondary changes or are results of idiopathic FSGS, might be needed. Also different treatment for MGN with coexisting FSGS lesions that vary in membranous stages may be required.

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