Nephrotic Syndrome Associated with Subacute Bacterial Endocarditis (SBE): A Case Report

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We experienced a female nephrotic patient associated with subacute bacterial endocarditis. Her proteinuria was completely normalized after antibiotic therapy and valve replacement. Immunofluorescence and an electron microscopic study of a renal biopsy specimen showed little evidence of immune complex in the glomeruli. Marked deposition of properdin in the glomeruli and the reduced level of serum complement may indicate involvement of the complement system in the pathogenic mechanism of massive proteinuria in this case.

(Key Words: Nephrotic syndrome, subacute bacterial endocarditis (SBE))

INTRODUCTION
Subacute bacterial endocarditis (SBE) is known to induce glomerulonephritis (GN). This type of GN is believed to be a prototype of immune complex mediated GN, which is caused by bacterial antigens and its related antibodies because of the presence of electron dense deposits in glomeruli from these patients. However, direct demonstration of bacterial antigen in the glomeruli has not been reported. Proteinuria is the most common manifestation of this GN and its precise mechanism is not well understood.

We experienced a nephrotic patient associated with SBE. Renal biopsy specimens showed scanty evidence of immune complex deposition in the glomeruli. The pathogenic mechanism of SBE related glomerulonephritis is discussed in this report.

CASE REPORT
A 38 year-old housewife was admitted to the Tokai University Hospital with complaints of high grade fever and lower leg edema on July 31, 1990. Although she had general fatigue and lower leg edema in June before admission, she did not consider that this condition was important, and did not consult a doctor at that time. Thereafter, she became febrile and consulted a doctor in July. Lower leg edema, petechia, hematuria, proteinuria and anemia were noted. Leukocytosis and strongly positive C-reactive protein (CRP) were also found, and she was referred to our hospital. Valve disease had been pointed out when she was 14 years old, but the precise onset and course could not be detected.

Vital signs on admission were a body temperature of 38.1°C, heart rate of 120 per minute with sinus rhythm, and blood pressure of 115/60 mmHg. Physical examination revealed facial flushing, anemic palpebral conjunctiva and marked edema in the lower extremities. However, no petechia in her skin and mucous membrane and no nodules in her fingers were found. Systolic murmur (Levine V/VI) was audible in the Erb area, and thrill was detected in the apex. Splenomegaly was found in the abdomen.

Laboratory findings were as follows: hemoglobin, 4.4 g/dl; hematocrit, 14.0%; urea nitrogen, 34.4 mg/dl; serum creatinine, 1.5 mg/dl; glomerular filtration rate (GFR), 22 ml/min; serum total protein, 5.4 g/dl; albumin, 2.2 g/dl; CRP, 9.69 mg/dl; rheumatoid factor, 62 IU/ml;

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antinuclear factor, 1+, speckled and diffuse pattern; IgG, 2,280 mg/dl; IgM, 281 mg/dl; C3, 20 mg/dl; C4, 7 mg/dl; and erythrocyte sedimentation rate, 130 mm/1hr and 145 mm/2hr. Urinalysis revealed 2+ occult blood and 3+ protein (4.5 g/day). Blood culture disclosed Lactococcus cremoris septicemia. Extensive vegetation around the mitral valve was pointed out by ultrasonic cardiology (UCG; Fig. 1).

Mitrail valve regurgitation and prolapse were probably caused by SBE. Ultrasonography and computed tomography (CT) showed splenomegaly. The size of the spleen was 124 x 62 mm by US and a small splenic infarction was found.

Needle renal biopsy was performed on August 13 to examine the renal complication responsible for her massive proteinuria. Light

![Ultrasonic cardiography showed large vegetation on the mitral valve.](image1)

![Renal biopsy specimen showed mild proliferative glomerulonephritis with small crescents.](image2)
microscopic findings showed no thickening of the capillary walls, but mild endocapillary proliferation and small crescents were noticed (Fig. 2). Immunofluorescence studies were as follows: IgG (−), IgM (+), IgA (−), properdin (2 +), C3 (1 +) and fibrinogen (−). Intense deposits of properdin (Fig. 3) were characteristic in this case. In an electron microscopic study, there were very few dense deposits in the basement membrane, and no deposits in the subepithelial or subendothelial space (Fig. 4).

The clinical course is depicted in Fig. 5. Steroid therapy (PSL 40 mg/day, orally) was first performed, but the dose had to be gradual-
Clinical Course  
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Fig. 5 Clinical course.

Prednisolone: 40mg 30mg

Renal Biopsy

C50 (U/ml)

CH50 10 1

C3 20 (mg/dl)

C4 7 (mg/dl)

RF 62 (U/ml)

MV Replacement

9/14

S-Alb (g/dl)

U-Prot (g/day)

8/10 8/20 8/30 9/10 9/20 9/30 10/10 10/20 10/30

Support the concept that persistent bacterial infection induces GN. However, no evidence of immune complex mediated GN was found in this case because we only observed scanty immunoglobulin deposits, and very few electron dense deposits, which are believed to be hallmarks of immune complex mediated glomerulonephritis.

Other pathogenic mechanisms should be considered to explain massive proteinuria. In this patient, rheumatoid factor (RF) was detected during the proteinuric phase and disappeared after remission. Rheumatoid factors were reported in the sera of approximately 50% of patients with SBE [9]. Miyazaki et al. reported that RFs might be involved in the development of some types of GN as a component of immune complex deposits in the glomeruli [6]. However, there was little evidence of immune complex deposits in this case because immunoglobulin and electron dense deposits were too small to support the immune complex mediated mechanism in the glomeruli.

Another pathogenic factor which might be responsible for massive proteinuria in this case is a T cell derived factor which has been proposed as a permeable factor of the glomerular basement membrane in the pathogenesis of the
minimal change nephrotic syndrome [4] although it has not been identified. We could not demonstrate this factor directly in this case. However, persistent bacterial infection may activate lymphocytes, both T cells and B cells. The consequence of B cell activation was reflected in the elevated serum IgG level, the transient rises of rheumatoid factor and antinuclear factor in this case. Unfortunately, good clinical or laboratory markers for T cell activation were not available, and direct demonstration of the involvement of T cell factor was not possible in this case. Further investigation is required to clarify the role of T cell factors in the development of proteinuria in such cases.

This patient showed hypocomplementemia. The levels of complement on admission were as follows: C3, 20 mg/dl; C4, 7 mg/dl and CH50, below 10 mg/dl. The causes of hypocomplementemia may be discussed from two aspects: hypoproduction, or overconsumption. The complement system might be involved in this case although immune deposits were not demonstrated. Intense properdin deposits in the glomeruli which are frequently observed in glomeruli from patients with toxemia of pregnancy may be one of the causes of proteinuria, because properdin is thought to play some role in the activation of the alternative pathway in the complement system. Since C3 deposition was also observed in this case, we have to consider the role of the alternative pathway. One factor in activating C3, which we call the C3 nephritc factor, depends on properdin [2], and the C3 nephritc factor and properdin stabilize C3bBb (alternative pathway C3 convertase). Moreover, the membrane attack complex (MAC), which consists of late component (C5b-9), should also be taken into consideration. Parra et al. reported that granular deposition of MAC was found in the glomerular capillary wall and mesangial region in human acute glomerular nephritis (AGN) [7]. It has also been reported that the formation of C5b-9 is one of the causes of proteinuria in experimental membranous nephropathy in rabbits [3], although its precise role in the human system is unknown. According to analyses by Williams and Kilpatrick, immunofluorescent stains for C3 and terminal complement complex of neoantigens (C5-9) were positive on the endocardial surface in patients with infective endocarditis (8). The same mechanism might apply in the renal tissue.

It was concluded from this case study that proteinuria might be induced by some unknown mechanism in addition to immune complex deposits in the glomeruli in SBE patients. Further study is necessary to clarify this point.

REFERENCES