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CASE REPORT

A case of immunoglobulin A nephropathy with a long history (32 years) in the relatively poor prognosis group

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Abstract
We report herein an immunoglobulin A nephropathy patient with a long history of 32 years in the relatively poor prognosis group according to pathological findings. In general, such cases in the relatively poor prognosis group develop end-stage renal failure, and undergo dialysis within 5 to 20 years. However, the period from the appearance of proteinuria to hemodialysis was very long in this patient. His mean blood pressure remained at approximately 100 mm Hg with the administration of some antihypertensive agent. The genotype of the angiotensin converting enzyme was II. Although normal renal function continued for the duration, he had severe acute tonsillitis at 45 and 49 years of age. After these infections, proteinuria and/or hematuria were exacerbated and he gradually progressed to end-stage renal failure. The good prognosis in this patient might be attributable to good control of blood pressure, whereas the decline in renal function might be attributable to severe recurrent upper respiratory tract infection. It seems that control of blood pressure and prevention of recurrent upper respiratory tract infection are important factors in the prognosis of patients with immunoglobulin A nephropathy. Although the association between angiotensin converting enzyme genotype and prognosis of immunoglobulin A nephropathy is controversial, it is postulated that angiotensin converting enzyme genotype II might be correlated with the good prognosis in this case.

Key words: Angiotensin converting enzyme gene polymorphism, Immunoglobulin A nephropathy, Reciprocal serum creatinine, Tonsillitis

中文摘要
本文報道一例病史長達32年的免疫球蛋白A腎病患者。根據其病理學檢查結果，患者屬預後較差組別。一般類預後較差的患者會出現末期腎臟衰竭，並在5至20年內需要接受透析。然而，本例患者從出現蛋白尿進展至接受血液透析的間隔時間非常長。在應用抗高血壓藥後，他的平均血壓穩定在約100 mm Hg的水平。血管緊張素轉換酶的基因型為II型。儘管在此期間其腎功能保持正常，但患者在45歲和49歲時發生了嚴重的急性扁桃腺炎。出現這些感染後，患者的蛋白尿和／或血尿加劇，並逐漸進展至末期腎臟衰竭。患者的預後較好可能是由於對血壓的控制較佳，而腎功能的下降則可能與嚴重復發性上呼吸道感染有關。由此看來，控制血壓和防止復發性上呼吸道感染是影響免疫球蛋白A腎病患者預後的重要因素。雖然血管緊張素轉換酶基因型和免疫球蛋白A腎病預後之間的聯繫尚存在爭議，我們認為血管緊張素轉換酶II可能與本例患者的良好預後有關。

INTRODUCTION
Patients with immunoglobulin (Ig) A nephropathy are classified into four groups at the time of renal biopsy according to a system developed by a joint committee of the Ministry of Health and Welfare of Japan and the Japanese Society of Nephrology (1). They are the good

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prognosis group, relatively good prognosis group, relatively poor prognosis group, and poor prognosis group. It is generally considered that development and exacerbation of IgA nephropathy are frequently preceded by episodes of recurrent upper respiratory tract infection. Certain viral antigens might be related to the upper respiratory tract infection in patients with IgA nephropathy. Hematuria and/or proteinuria are usually exacerbated after upper respiratory infections (2).

We experienced a patient with IgA nephropathy who had a good prognosis despite being classified in the relatively poor prognosis group according to pathological findings.

CASE REPORT

A 31-year-old man was admitted to Juntendo University Hospital for investigation of microscopic hematuria and proteinuria on 7 February 1974. When he was 26 years old, proteinuria was pointed out in a medical checkup, but he did not have another checkup for 5 years. He had no remarkable medical or familial history.

On physical examination, his blood pressure was 130/70 mm Hg in the supine position. Pharyngeal tonsils showed slight swelling. There was no evidence of peripheral edema or purpura. Levels of urinary protein excretion were 272 mg/dL, and 24-hour urinary protein excretion was 2.2 g. Urinary sediments showed a few red blood cells with hyaline and granular casts. Initial laboratory findings are shown in Table 1. In peripheral blood, hemoglobin was 14.9 g/dL, red blood cells 468 x 10^4/μL, and white blood cells 5300/μL. The blood urea nitrogen was 21 mg/dL, serum creatinine (s-Cr) 1 mg/dL, total protein 7.4 g/dL, and serum albumin 4.5 g/dL. The titers of antistreptolysin and antistreptokinase were 160 TU and 2560 times, respectively. The 50% complement hemolytic units level in sera was within normal limits. The creatinine clearance was 79.8 mL/min. Urine cultures were negative for mycobacteria.

A renal biopsy was performed on February 19, 1974. Four of 19 glomeruli were globally sclerosed. One glomerulus showed adhesion to Bowman's capsule. Three glomeruli showed marked proliferation of mesangial cells and focal para-mesangial deposits in the mesangial areas. Interstitial fibrosis and lymphocyte infiltration were observed over a 20% area of the renal cortex (Fig. 1). In immunofluorescence, IgA, IgG, and C3 were deposited in the glomerular mesangial areas. The genotype of the angiotensin converting enzyme (ACE) polymorphism was II, as shown in Figure 2.

Commonly, it is recognized that reciprocal s-Cr concentration correlates linearly with progression of chronic renal failure (3). This analysis may help to estimate the progression of the disease. Changes of reciprocal s-Cr levels in our patient from the first medical examination in Juntendo University Hospital to the present are shown in Figure 3. The slope of reciprocal s-Cr levels is divided into three parts. The first slope indicates renal function from the beginning of the

Table 1. Laboratory data at first admission to the Juntendo University Hospital.

Laboratory tests	Results
Hematologic test	
WBC	5300/μL
RBC	468 x 10^4/μL
Hemoglobin	14.9 g/dL
Hematocrit	42.8%
Platelet	21 x 10^4/μL
ESR	3 mm/hour
Serological test	
CRP test	(-)
CH50	26.3
Antistreptolysin	160 TU
Antistreptokinase	2560 times
Biochemical test	
Total protein	7.4 g/dL
Albumin	4.5 g/dL
AST	19 U
ALT	13 U
LDH	210 U
ALP	50 U
BUN	21 mg/dL
Creatinine	1 mg/dL
Uric acid	6 mg/dL
Na	146 mEq/L
K	4.1 mEq/L
Cl	107 mEq/L
Ca	4.9 mEq/L
P	3.7 mg/dL
Total cholesterol	167 mg/dL
Triglycerides	114 mg/dL
Urinalysis	
Protein	2.2 g/day
Sugar	(-)
Sediments	
WBC	1-5/HPF
RBC	5-10/HPF
Casts	Hyaline (+)
	Granular (+)
Renal function	
CCr	79.8 mL/min

WBC = white blood cell count; RBC = red blood cell count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CH50 = 50% complement hemolytic units; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; ALP =alkaline phosphatase; BUN = blood urea nitrogen; HPF = high power field; CCr = creatinine clearance

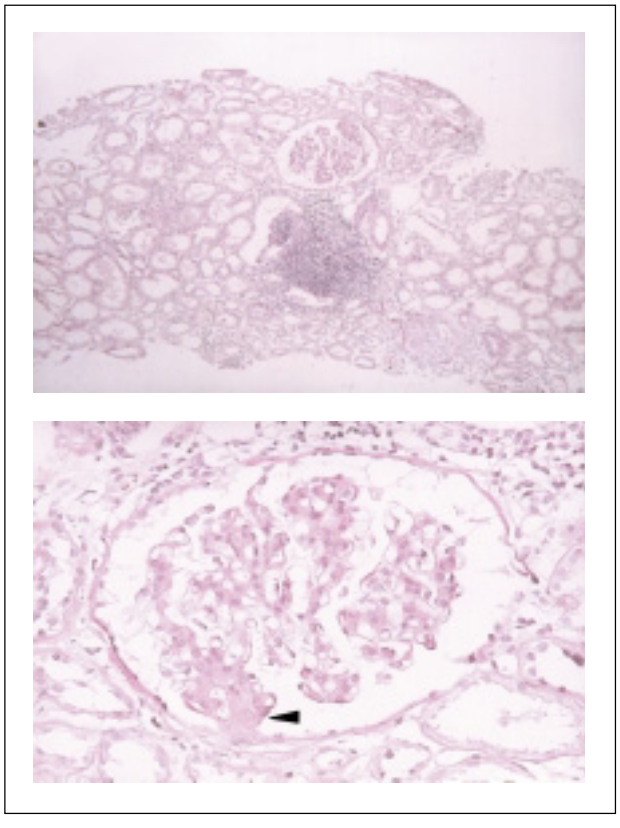

Figure 1. (A) Light-microscopic findings. Glomerular sclerosis and interstitial lymphocyte infiltrations were observed. Periodic acid-Schiff staining 100x. **(B)** Focal-segmental proliferation of mesangial cells and mesangial matrix expansion, and focal adhesion to Bowman's capsules (arrow) were observed. Periodic acid-Schiff staining 400x.

Figure 2. Electrophoresis in agarose gel. Genomic DNA was extracted from whole blood and then polymerase chain reaction was performed. The angiotensin converting enzyme II genotype was determined by the presence of the 500 base pair fragment (1).

observations to 19 years. It shows stable renal function. The patient had been treated with dipyridamole (150 mg/day) from 1985 (17 years from the first medical examination in Juntendo University Hospital). Thereafter, the levels of urinary protein excretion decreased to 76 mg/dL. However, urinary sediments showed granular casts, white blood cell casts, and red blood cell casts. The second slope indicates his renal function from 19 to 24 years. He had a severe upper respiratory infection in December 1987 (19 years). Proteinuria and hematuria were exacerbated after the

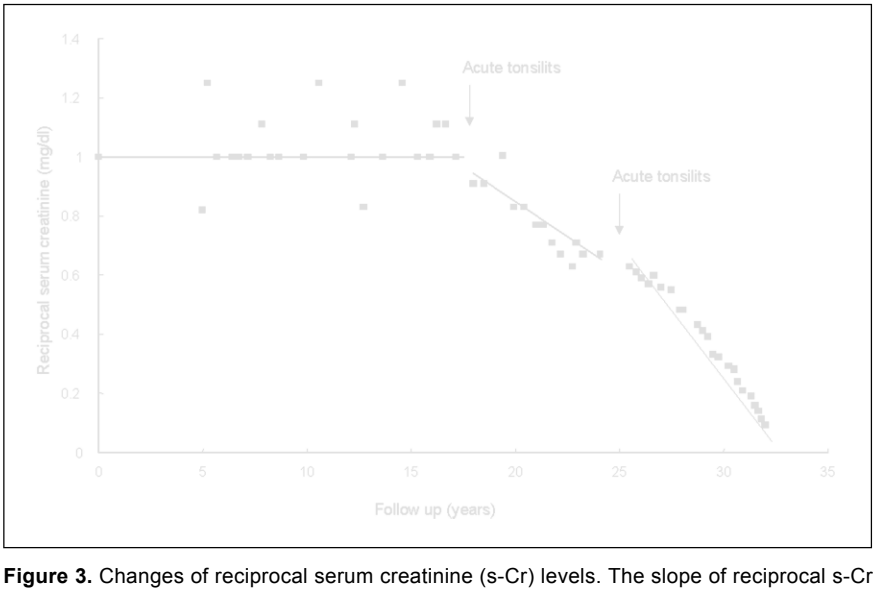

Figure 3. Changes of reciprocal serum creatinine (s-Cr) levels. The slope of reciprocal s-Cr levels was divided into three parts.

severe infection. The level of urinary protein excretion was 1020 mg/dL. Urinary sediments showed 20 to 25 red blood cells/high power field. The levels of s-Cr were also increased by the infection. After 24 years, the slope of reciprocal s-Cr had decreased markedly because of the second severe upper respiratory tract infection (Fig. 3). He had a severe recurrent upper respiratory infection in September 1992 (24 years) with proteinuria and microscopic hematuria exacerbated in the same way. Urinalysis showed urinary protein excretion of 479 mg/dL and 20 to 25 red blood cells/high power field in the sediments. During both severe infections, the patient was administered several antibiotics and antipyretics, such as ampicillin, cefteram pivoxil, or sulindac for several days.

Although his blood pressure remained in good control (mean blood pressure approximately 100 mm Hg) until 23 years without any antihypertensive agents (Fig. 4), it was gradually increased because of exacerbation of renal function. He was not treated with ACE inhibitors because treatment with such drugs was not used for non-hypertensive patients with IgA nephropathy. Finally, he was given the antihypertensive nilvadipine (2 mg/day), in 1997 (28 years after initial presentation). The levels of blood pressure were approximately 150/96 mm Hg at that time. Because all therapy was ineffective, he progressed to end-stage renal failure (ESRF), and was placed on hemodialysis 24 June 2000 (32 years after initial presentation). However, we could not perform re-biopsy of renal tissues because of his disagreement.

DISCUSSION

Immunoglobulin A nephropathy was initially described as one type of glomerulonephritis with a good prognosis (4). However, progression to ESRF including hemodialysis or continuous ambulatory peritoneal dialysis is not as rare as originally thought. Progressive and/or exacerbating factors reported previously for this disease have been male sex, old age, hypertension, massive proteinuria, and prolonged duration (5). Recurrent upper respiratory tract infection is also an important factor of poor prognosis (2).

Histologically, mesangial cell proliferation and increased extracellular matrix, glomerulosclerosis, crescent formation or adhesion to Bowman's capsules, interstitial fibrosis, and vascular sclerosis are factors for poor prognosis in patients with IgA nephropathy (4,6,7). Patients with IgA nephropathy are classified into the following four groups at the time of renal biopsy according to the criteria of the joint committee of the Ministry of Health and Welfare of Japan and the Japanese Society of Nephrology (1): 1. good prognosis group: almost no possibility of dialysis; 2. relatively good prognosis group: possibility of dialysis is relatively low; 3. relatively poor prognosis group: dialysis is likely to be required within 5 to 20 years; and 4. poor prognosis group: the possibility of dialysis within 5 years is high. Among such clinical guidelines of IgA nephropathy, the light-microscopic findings can be summarized as follows: (a) Glomerular findings: 1. good prognosis group: slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule are not observed; 2. relatively good prognosis group: slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule seen in less than 10% of all biopsied glomeruli; 3.

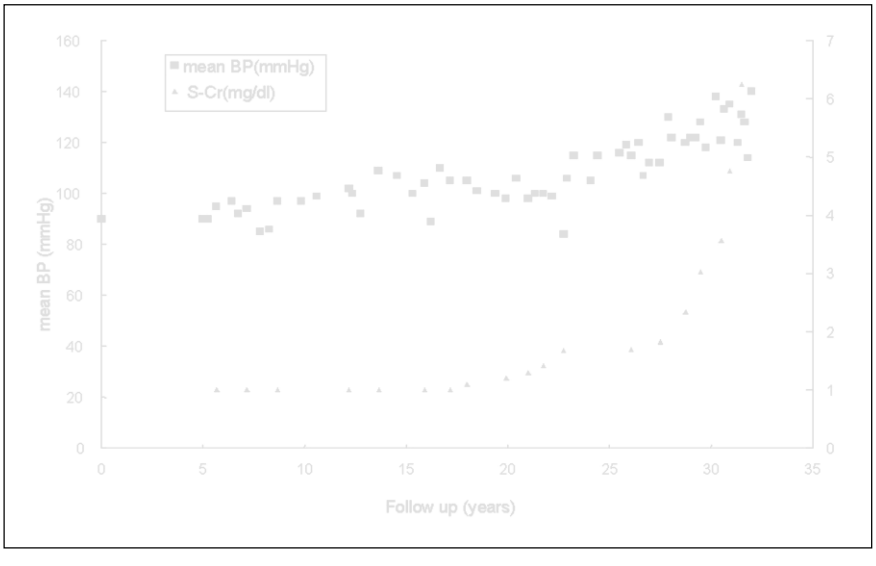

Figure 4. Mean blood pressure (squares) and serum creatinine (s-Cr) level (triangles) during the observation period.

relatively poor prognosis group: moderate, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule seen in 10% to 30% of all biopsied glomeruli; and 4. poor prognosis group: severe, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule seen in more than 30% of all biopsied glomeruli. When sites of sclerosis are totaled and converted to global sclerosis, the sclerosis rate is more than 50% of glomeruli. Some glomeruli also show compensatory hypertrophy. The sclerosis rate is the most important of these indices for evaluation of prognosis. (b) Interstitial and vascular findings: 1. good prognosis group: prominent changes are not seen in the interstitium, renal tubuli, or blood vessels; 2. relatively good prognosis group: same as above; 3. relatively poor prognosis group: cellular infiltration is slight in the interstitium except around some sclerosed glomeruli. Tubular atrophy is slight, and mild vascular sclerosis is observed; and 4. poor prognosis group: interstitial cellular infiltration, tubular atrophy, and fibrosis are seen. Hyperplasia or degeneration may be seen in some intrarenal arteriolar walls (1).

This patient was diagnosed as in the relatively poor prognosis group, because poor prognostic findings were recognized histologically. Accordingly, moderate mesangial cell proliferation and increased matrix were shown. Glomerulosclerosis and adhesion to Bowman's capsule were seen in 25% of all biopsied glomeruli, in addition to interstitial cellular infiltration. Furthermore, urinary sediments have shown white blood cell casts, red blood cell casts, and granular casts from the early stage of follow-up duration. It is generally considered that dialysis will be required within 5 to 20 years (1). According to the Haas grading system, this patient was diagnosed as subclass III (8). Renal survival in cases with crescents and/or interstitial inflammatory cell infiltrations was significantly worse than in cases without them in subclass III. According to Haas, more than 50% of patients in subclass III with crescents and/or interstitial inflammatory cell infiltration will require dialysis or renal transplantation within 10 years from the date of biopsy (8). However, this case showed a long duration of 32 years from the appearance of proteinuria to hemodialysis.

In this case, the patient showed a good prognosis although his renal histological findings had already progressed at the time of renal biopsy. His mean blood pressure levels were well controlled (approximately 100 mm Hg) for a long period with administration of some antihypertensive agent. Strict control of blood pressure is one of the most important factors for good prognosis in patients with IgA nephropathy. The common international strategy adopted at present is based on blood pressure control by administration of antihypertensive agents in addition to appropriate physical exercise and dietary protein restrictions (9). However, this patient had practiced no physical exercise or diet therapy. It is suggested that, essentially, strict control of blood pressure contributed to his good prognosis.

Several recent studies have shown a significant association between ACE gene polymorphism and progression to ESRF in patients with IgA nephropathy (10,11). It has been reported that the rate of reduction of renal function in patients with the DD or ID genotype of ACE was significantly higher than that of patients with the II genotype (10). However, several studies have reported that no association was observed between insertion/deletion polymorphism of the ACE gene and renal progression in IgA nephropathy (12,13). The ACE polymorphism genotype of this patient was II, which is postulated as a possible reason for the good prognosis. The main exacerbating factor for his renal function might be severe recurrent upper respiratory tract infections. After severe infections, his renal function deteriorated, and hematuria, proteinuria, and s-Cr levels were exacerbated. The titers of antistreptolysin and antistreptokinase after tonsillitis were within normal limits, and the number of eosinophils in peripheral blood did not increase. Therefore, the possibility of poststreptococcal glomerulonephritis and/or allergic interstitial nephritis seemed to be ruled out. Because his blood pressure became uncontrollable in recent years, his renal function deteriorated further.

In conclusion, it seems that severe recurrent upper respiratory tract infection is an important prognostic factor in patients with IgA nephropathy. Strict control of blood pressure, prevention of upper respiratory tract infection, and its treatment at an early stage are important in patients with IgA nephropathy.

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