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A Case of Nephrotic Syndrome with Rapid Spontaneous Remission in an Elderly Patient

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ABSTRACT

In July 1994, a 70-year-old woman was diagnosed as having nephrotic syndrome with proteinuria of 8 to 10 g/day and a serum albumin level of 1.8 g/dl. She was hospitalized in August 1994 for investigation. The urinary findings then normalized, with urinary protein and occult blood both negative and total urinary protein excretion at 0 g/day. A renal biopsy was performed, and spontaneous remission of minimal change nephrotic syndrome was diagnosed. This is an interesting case involving rapid remission of minimal change nephrotic syndrome in an elderly patient.

Key words: *Minimal change nephrotic syndrome, Elderly onset, Spontaneous remission*

Elderly onset nephrotic syndrome is usually a secondary disease and is often intractable. Here we describe an elderly patient who showed rapid spontaneous remission of minimal change nephrotic syndrome.

CASE REPORT

A 70-year-old woman noticed dark urine on June 10, 1994, and attended a local urologist who found proteinuria. On July 4, she was admitted to Mihara City Medical Association Hospital and nephrotic syndrome was diagnosed with a urinary protein loss of 8–10 g/day and a serum albumin level of 1.8 g/dl. She was referred to the Department of Internal Medicine at Onomichi General Hospital on July 22. Urinalysis showed that urinary protein was (4+) and occult blood was (±). Serum total protein was 7.6 g/dl, albumin was 2.6 g/dl, and total cholesterol was 368 mg/dl. These findings were consistent with a diagnosis of nephrotic syndrome. She was hospitalized on August 17 for further investigation.

Findings on admission to Onomichi General Hospital: She was 140 cm tall, weighed 51.5 kg, and had a blood pressure of 126/86 mmHg and a pulse rate of 72/min (regular). There were no abnormalities of the heart, lungs, or abdomen, and no edema of the extremities.

Laboratory findings on admission to Mihara City Medical Association Hospital (Table 1): Urinalysis showed heavy proteinuria. Urinary Bence – Jones protein was negative. Although the serum total protein level was normal at 7.0 g/dl, there was marked hypoalbuminemia (1.8 g/dl). Protein electrophoresis showed that albumin was low, while the alpha-2-globulin and gamma-globulin levels were high. Immunoglobulin levels were also high, with an IgG of 3822 mg/dl, IgA of 651 mg/dl, and IgE 740 U/ml. Renal function was normal. The patient was diagnosed as having nephrotic syndrome from the above findings. However, the etiology of her nephrotic syndrome was unknown.

Laboratory findings on admission to Onomichi General Hospital (Table 2): Urinalysis showed that urinary protein and occult blood were negative, with the total urinary protein loss being 0 g/day. She had mild hypoalbuminemia, with a total protein level of 7.1 g/dl and an albumin level of 3.5 g/dl, but there had been an improvement when compared with the previous data. The IgG level was high (2390 mg/dl) as was the IgA level (459 mg/dl), but both values were lower than before.

Clinical course (Table 3): Her urinalysis findings showed an improvement and the serum albumin level increased. However, a renal biopsy was performed on August 23, because secondary nephrotic syndrome was suspected. The histological specimen contained eight glomeruli. There was no mesangial cell proliferation or matrix expansion, although prominent changes were

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Table 1. Laboratory findings on admission to Mihara City Medical Association Hospital

Urinalysis		T-Bil	0.3 mg/dl
pH	6.0	GOT	27 IU/liter
Albumin	(4+)	GPT	26 IU/liter
Glucose	(±)	LDH	506 IU/liter
Blood	(+)	ZTT	22.2 KU
Sediment		TC	172 mg/dl
RBC	2~4/HPF	BS	111 mg/dl
WBC	3~5/HPF	BUN	15.1 mg/dl
Casts	(+)	Cr	1.0 mg/dl
Daily urinary protein	8~10 g/day	UA	6.4 mg/dl
Urinary Bence-Jones protein	(−)	Na	138 mEq/liter
Peripheral blood findings		K	3.8 mEq/liter
WBC	4750/mm^3	Cl	105 mEq/liter
RBC	395×10^4/mm^3	Serological data	
Hb	13.2 g/dl	CRP	0.5 mg/dl
Ht	40.4%	RA	(+)
Plt	21.4×10^4/mm^3	Wa-R (RPRCT)	(−)
ESR	156 mm/h	TPHA	(−)
Coagulation data		HBsAg	(−)
PT	117%	HCVAb	(−)
aPTT	33.5 sec	Immune function	
Fbg	468 mg/dl	IgG	3822 mg/dl
FDP	5 μg/ml	IgA	651 mg/dl
Biochemical data		IgM	121 mg/dl
TP	7.0 g/dl	IgE	740 U/ml
Alb	25.9%	ANA	(−)
α1-gl	2.5%	Renal function	
α2-gl	10.6%	Ccr	90 liters/day
β-gl	8.9%		
γ-gl	52.1%		
Alb	1.8 g/dl		

found in the glomerular basement membrane (Fig. 1). Using the fluorescent antibody method, IgG, IgA, IgM, C3, C4 and fibrinogen were all negative. Electron microscopy showed foot process effacement and a thinning of the glomerular basement membrane (Fig. 2). Subendothelial thickening of the glomerular basement membrane, focal mesangial interposition, and tortuosity were also detected, but these changes were considered to be due to aging. Based on these findings, spontaneous remission of minimal change nephrotic syndrome was diagnosed. After discharge from hospital, the case was followed up and no recurrence was noted.

DISCUSSION

Spontaneous remission of minimal change nephrotic syndrome (MCNS) is known to occur after viral infections such as rubeola or varicella or when the syndrome arises due to treatment with nonsteroidal anti-inflammatory agents and the offending drug is withdrawn[14]. However, this patient had no cold-like symptoms and no history of using nonsteroidal anti-inflammatory agents.

Since MCNS shows a good response to steroids and since spontaneous remission occurs in the circumstances described above, it appears that its etiology involves abnormalities of T cell function[16,18]. For example, it has been shown that suppressor cell activity is enhanced by *in vitro* studies involving concanavalin A stimulation of

Table 2. Laboratory findings on admission to Onomichi General Hospital

Urinalysis		LDH	442 IU/liter
pH	6.0	ZTT	17.1 KU
Albumin	(−)	TC	262 mg/dl
Glucose	(−)	BS	95 mg/dl
Blood	(−)	BUN	6.4 mg/dl
Sediment		Cr	0.6 mg/dl
RBC	1~2/HPF	UA	5.9 mg/dl
WBC	2~3/HPF	Na	142 mEq/liter
Casts	(−)	K	4.6 mEq/liter
Daily urinary protein	0 g/day	Cl	105 mEq/liter
Peripheral blood findings		Ca	4.7 mEq/liter
WBC	6400/mm^3	P	3.3 mg/dl
RBC	424×10^4/mm^3	Serological data	
Hb	13.5 g/dl	CRP	0.10 mg/dl
Ht	40.8%	RF	<17.5 IU/ml
Plt	23.6×104/mm^3	Wa-R (RPRCT)	(−)
ESR	87mm/h	TPHA	(−)
Coagulation data		HBsAg	(−)
PT	100%	HCVAb	(−)
APTT	23.2 sec	Immune function	
Fbg	387 mg/dl	IgG	2390 mg/dl
FDP	<10 μg/ml	IgA	459 mg/dl
uFDP	<0.1 μg/ml	IgM	136 mg/dl
Biochemical data		C3	96.5 mg/dl
TP	7.1 g/dl	C4	42.8 mg/dl
Alb	51.3%	CH50	35.1 U/ml
α1-gl	2.1%	DNA	4 U/ml
α2-gl	11.3%	ANA	<×20
β-gl	10.9%	CIC	<1.5 μg/ml
γ-gl	24.4%	Renal function	
Alb	3.5 g/dl	Ccr	87.9 ml/min
T-Bil	0.65 mg/dl	Blood β2-MG	2.6 μg/ml
GOT	31 IU/liter	Urine β2-MG	5.6 μg/h
GPT	31 IU/liter	NAG	24.0 mU/h

peripheral blood lymphocytes from pediatric patients with MCNS[10]. However, some investigators have demonstrated that the abnormalities of T cell function in MCNS are also present in nephrotic syndrome caused by other glomerular diseases, and have concluded that such abnormalities are a consequence of the nephrotic syndrome[7,19]. Moreover, other investigators have found that lymphocyte subpopulations show no significant differences in MCNS patients compared with normal controls[3]. Thus, there is no clear consensus on the changes of T cell subsets in this disease. Unfortunately, T cell subsets were not measured in our patient.

Immunoglobulin production by unstimulated B cells from MCNS patients is often increased and the number of circulating B cells also show an increase[1]. Despite this, serum immunoglobulin levels are low in MCNS and this is unlikely to be due to urinary excretion[5], suggesting that secondary inhibition of B cells occurs following an increase of suppressor T cell activity[1]. However, our patient had high levels of IgG, IgA, and IgE in the active stage of the nephrotic syndrome,

Table 3. Clinical course

	94/7/4	94/7/22	94/8/18
Urinalysis			
Albumin	(4+)	(4+)	(−)
Glucose	(±)	(−)	(−)
Blood	(+)	(±)	(−)
Daily urinary Protein (g/day)	8～10		0
Biochemical data			
TP (g/dl)	7.0	7.6	7.1
Alb (g/dl)	1.8	2.6	3.5
TC (mg/dl)	172	368	262
BUN (mg/dl)	15.1	17.1	6.4
Cr (mg/dl)	1.0	0.8	0.6
UA (mg/dl)	6.4	6.8	5.9

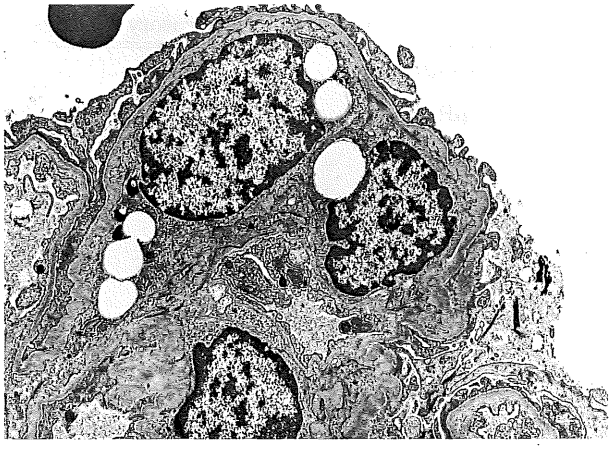

Fig. 2. Electron micrograph of the same tissue (×9500).
Foot process effacement and thinning of the glomerular basement membrane can be seen.

while IgG and IgA tended to decrease in remission. The pathological significance of these findings is not clear, but such changes in the immunoglobulins might be involved in the spontaneous remission of MCNS. Neuhaus et al reported the activation of CD4-positive Th cells in the initial stage of steroid-sensitive nephrotic syndrome and stated that this change was directly related to the nephrotic syndrome itself[12]. They reported that the percentage of CD4-positive cells expressing the activation marker CD25 (the α-chain of the interleukin (IL)-2 receptor) was increased significantly when compared with during remission, and that these findings were also seen in the urine. They also found a significant increase of IL-2 and IL-4 in culture supernatant when the peripheral blood mononuclear cells of patients with steroid-sensitive nephrotic syndrome were stimulated by calcium ionophore and phorbol myristate acetate, and they concluded that the activation of T cells is important in relapse of the nephrotic syndrome in these patients[13]. Among other cytokines, Daniel et al found that the levels of IL-1α, IL-1β, IL-1 receptor antagonist, and tumor necrosis factor α were normal, while IL-8 was reduced in patients with steroid-sensitive nephrotic syndrome when compared with controls[2]. When the changes in the immunoglobulins of such patients were examined, it was found that CD4-positive Th cells were activated for some reason at the onset of the nephrotic syndrome so that immunoglobulin levels increased. However, it appears that this change is rapidly reversed if the activation of CD4-positive Th cells is controlled after which immunoglobulins tend to decrease, i.e., since the active stage of the nephrotic syndrome is short, the amount of immunoglobulin eliminated in the urine is low. Therefore, the level of immunoglobulins is high in the active period but decreases with remission, and it is possible that these changes in the immunoglobulins reflect the activation of CD4-positive Th cells. However, the etiology of the nephrotic syndrome in our patient was unclear. The T cell subsets, CD25 expression, and cytokine levels were not determined in our patient, so further study is required in the future.

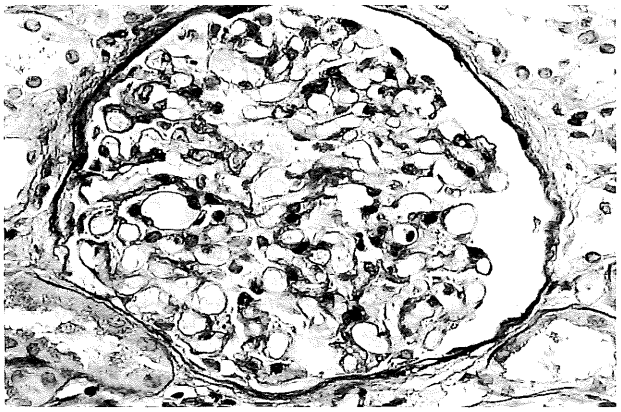

Fig. 1. Light micrograph of the renal biopsy specimen (PAS ×450).
There is no mesangial cell proliferation or matrix expansion. Thickening of the glomerular basement membrane is also not seen.

In elderly patients, the nephrotic syndrome is often a secondary disease that is resistant to treatment and has a poor prognosis[4,6,8,11,20]. Membranous nephropathy and MCNS are important causes of primary nephrotic syndrome in the elderly. The complete remission rate for primary

MCNS in elderly individuals is 80 to 90%, which is similar to that in younger patients. The diastolic blood pressure and serum creatinine tend to be higher than in younger patients, but it has also been reported that the elderly have better spontaneous remission rates and recurrence rates[8,17]. Recurrence occurs in about 18% of patients, but the response to retreatment is good. The percentage of patients finally progressing to renal failure is 5 to 6% and death occurs in 10 to 15% of those progressing to renal failure, but almost all deaths are due to cardiovascular complications or infection[17]. Because of the potentially good response to treatment, careful consideration must be given to patient management.

Our patient was a 70-year-old woman. Although the urinalysis findings improved and serum albumin tended to increase after admission, a renal biopsy was still performed because secondary nephrotic syndrome was suspected. It is reasonable to perform biopsy in elderly patients, since it has been reported that enough tissue for diagnosis can be obtained in 80 to 95% of elderly subjects if the investigator is experienced. The frequency of complications of biopsy is reported as 2.2 to 9.8%[15] and age is not a factor in the occurrence of complications[9]. Accordingly, in elderly patients like ours with nephrotic syndrome, renal biopsy should be actively considered to make a firm diagnosis of the underlying disease.

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REFERENCES

1. **Beale, M.G., Nash, G.S., Bertovich, M.J. and MacDermott, R.P.** 1983. Immunoglobulin synthesis by peripheral blood mononuclear cells in minimal change nephrotic syndrome. Kidney Int. **23:** 380–386.
2. **Daniel, V., Trautmann, Y., Konrad, M., Nayir, A. and Schärer, K.** 1997. T-lymphocyte populations, cytokines and other growth factors in serum and urine of children with idiopathic nephrotic syndrome. Clin. Nephrol. **47:** 289–297.
3. **Feehally, J., Beattie, T.J., Brenchley, P., Coupes, B., Postlethwaite, R.J., Houston, I.B. and Mallick, N.P.** 1983. T lymphocyte subpopulations and lymphocyte function in minimal change nephropathy (MCN) during long term remission. Eur. J. Paediatr. **140:** 158.
4. **Gertz, M.A., Kyle, R.A. and O'Fallon, W.M.** 1992. Dialysis support of patients with primary systemic amyloidosis. Arch. Intern. Med. **152:** 2245–2250.
5. **Giangiacomo, J., Cleary, T.G., Cole, B.R., Hoffsten, P. and Robson, A.M.** 1975. Serum immunoglobulin in the nephrotic syndrome-a possible cause of minimal change nephrotic syndrome. N. Engl. J. Med. **293:** 8–12.
6. **Kingswood, J.C., Banks, R.A., Tribe, C.R., Owen-Jones, J. and Mackenzie, J.C.** 1984. Renal biopsy in the elderly: clinicopathological correlations in 143 patients. Clin. Nephrol. **22:** 183–187.
7. **Kobayashi, K., Yoshikawa, N. and Nakamura, H.** 1994. T-cell subpopulations in childhood nephrotic syndrome. Clin. Nephrol. **41:** 253–258.
8. **Levison, S.P.** 1990. Renal disease in the elderly: the role of the renal biopsy. Am. J. Kidney Dis. **16:** 300–306.
9. **Marwah, D.S. and Korbet, S.M.** 1996. Timing of complications in percutaneous renal biopsy: What is the optimal period of observation? Am. J. Kidney Dis. **28:** 47–52.
10. **Matsumoto, K., Osakabe, K., Katayama, H. and Hatano, M.** 1982. *In vitro* lymphocyte dysfunction in lipoid nephrosis mediated by suppressor cells. Nephron **32:** 270–272.
11. **Moorthy, A.V. and Zimmerman, S.W.** 1980. Renal disease in the elderly: clinicopathologic analysis of renal disease in 115 elderly patients. Clin. Nephrol. **14:** 223–229.
12. **Neuhaus, T.J., Shah, V., Callard, R.E. and Barratt, T.M.** 1995. T-lymphocyte activation in steroid-sensitive nephrotic syndrome in childhood. Nephrol. Dial. Transplant. **10:** 1348–1352.
13. **Neuhaus, T.J., Wadhwa, M., Callard, R. and Barratt, T.M.** 1995. Increased IL-2, IL-4 and interferon-gamma (IFN-γ) in steroid-sensitive nephrotic syndrome. Clin. Exp. Immunol. **100:** 475–479.
14. **Nolasco, F., Cameron, J.S., Heywood, E.F., Hicks, J., Ogg, C. and Williams, D.G.** 1986. Adult-onset minimal change nephrotic syndrome: A long-term follow-up. Kidney Int. **29:** 1215–1223.
15. **Rakowski, T.A. and Winchester, J.F.** 1986. Renal biopsy in the elderly patient, p.37–39. *In* M.F. Michelis, B.B. Davis and H.G. Preuss (eds.), Geriatric nephrology, Field, Rich and Associates, New York.
16. **Sasdelli, M., Rovinetti, C., Cagnoli, L., Beltrandi, E., Bardoni, F. and Zucchelli, P.** 1980. Lymphocyte subpopulations in minimal-change nephropathy. Nephron **25:** 72–76.
17. **Schena, F.P. and Cameron, J.S.** 1988. Treatment of proteinuric idiopathic glomerulonephritides in adults: a retrospective survey. Am. J. Med. **85:** 315–326.
18. **Shalhoub, R.J.** 1974. Pathogenesis of lipoid nephrosis: A disorder of T-cell function. Lancet **2:** 556–560.
19. **Taube, D., Brown, Z. and Williams, D.G.** 1984. Impaired lymphocyte and suppressor cell function in minimal change nephropathy, membranous nephropathy and focal glomerulosclerosis. Clin. Nephrol. **22:** 176–182.
20. **Zech, P., Colon, S., Pointet, P.H., Deteix, P., Labeeuw, M. and Leitienne, P.H.** 1982. The nephrotic syndrome in adults aged over 60: etiology, evolution and treatment of 76 cases. Clin. Nephrol. **18:** 232–236.