Serum Levels of Soluble Interleukin-2 Receptor in Patients with Various Renal Diseases

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SUGIMOTO, H., HASHIMOTO, N., SUZUKI, S. and GEJYO, F. *Serum Levels of Soluble Interleukin-2 Receptor in Patients with Various Renal Diseases*. Tohoku J. Exp. Med., 1998, **184** (4), 311–316 ——— To clarify the serum levels of soluble interleukin-2 receptor (sIL-2R) in patients with renal diseases, we examined 281 patients with various renal diseases with or without systemic disease (including 197 patients without systemic diseases and 84 patients with systemic diseases). The sIL-2R level was significantly higher in patients with renal diseases, than in healthy volunteers. In the group of renal diseases, the sIL-2R level in patients with rapidly progressive nephritic syndrome was especially higher than in patients with other renal diseases. In patients without systemic diseases, the serum level of sIL-2R was significantly and positively correlated with the urinary excretion of protein, and the serum levels of creatinine and uric acid, and was negatively correlated with the glomerular filtration rate (GFR). In the patients with systemic diseases, the correlation between the serum levels of sIL-2R and the serum levels of creatinine or GFR were not as strong as observed in the patients without systemic diseases. The serum level of sIL-2R was outside the normal range in patients with systemic diseases with a serum level of creatinine above 2.0 mg/100 ml. These findings suggest that the serum levels of sIL-2R in patients with renal disease may increase and correlate with the impaired renal function, that the increased sIL-2R levels in patients with systemic diseases may be dependent on the activity of systemic disease, and that it may be not useful indicator of diseases activity in patients with systemic diseases when the serum level of creatinine was above 2.0 mg/100 ml. ——— soluble interleukin-2 receptor (sIL-2R); renal diseases; renal function © 1998 Tohoku University Medical Press

Soluble interleukin-2 receptor (sIL-2R) (Rubin et al. 1985; Nelson et al. 1986), which is released into blood when T cells are activated, is a marker of the activity of T-cell malignancies (Mackeen et al. 1986). We previously reported the serum level of sIL-2R to be useful in evaluating the activity of autoimmune

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diseases, and showed that it is significantly higher in patients receiving hemodialysis than in normal volunteers (Sugimoto et al. 1996a). We investigated between the serum level of sIL-2R in patients with various renal diseases with or without systemic diseases.

MATERIALS AND METHODS

Patients

Patients with various renal diseases ($n = 281$) were classified into groups based on whether or not they had systemic diseases (Table 1). Systemic diseases (group A) were classified according to WHO criteria (Glassock et al. 1996). The control group consisted of 40 healthy volunteers (20 male, 20 female; age 32.2 ± 4.7 years) with normal serum levels of Na, Cl, K, total protein, albumin, inorganic P, uric acid, creatinine and urea nitrogen, and normal urinalysis results.

Measurement of the serum level of sIL-2R

The serum level of sIL-2R was measured automatically with a solid-phase EIA kit (Cell Free IL-2R; Yamanouchi Pharmaceutical Co., Ltd., Tokyo) according to the method (Sugimoto et al. 1996b) as reported using an automatic EIA apparatus (Poseidon II; Aloka, Tokyo).

Statistical analysis

All numerical data were expressed as the mean $\pm$ standard deviation (s.d.). Significant difference was assessed using the unpaired *t*-test. Simple linear correlation was used to examine correlations between variables. A value of $p < 0.05$ was considered significant.

TABLE 1. *Patients with renal diseases*

Group	Renal disease	Number (M/F)	Age (years) (mean $\pm$ s.d.)
A	Acute nephritic syndrome	5(3/2)	36.4 ± 15.5
	Rapidly progressive nephritic syndrome	9(8/1)	61.8 ± 9.7
	Chronic nephritic syndrome	145(79/66)	36.6 ± 14.0
	Recurrent or persistent hematuria	6(3/3)	23.3 ± 8.4
	Nephrotic syndrome	32(22/10)	47.8 ± 17.9
B	Rheumatoid arthritis	7(3/4)	50.4 ± 12.4
	Systemic lupus erythematosus	48(4/44)	34.4 ± 13.5
	Sjögren's syndrome	3(0/3)	42.0 ± 5.3
	Progressive systemic sclerosis	4(0/4)	43.3 ± 6.7
	Mixed connective tissue disease	5(0/5)	26.2 ± 7.3
	Diabetes mellitus	17(11/6)	61.8 ± 11.9

Group A, patients without systemic diseases; Group B, patients with systemic diseases.

RESULTS

sIL-2R levels in healthy volunteers

The sIL-2R level in the control group was 301.5 ± 56.6 U/ml. The normal range was defined as mean ± 2 s.d. (188.3–414.7 U/ml).

sIL-2R levels in patients with various renal diseases

The sIL-2R level in patients with renal diseases was 547.7 ± 561.7 U/ml. The sIL-2R level was significantly higher in patients with both groups than in the healthy control group ($p < 0.01$) and was significantly higher in patients with rapidly progressive nephritic syndrome than in the other patients without systemic diseases in group A ($p < 0.05$) (Fig. 1).

In group B, the sIL-2R level was significantly higher in patients with mixed connective tissue disease (MCTD) than in patients with rheumatoid arthritis (RA) ($p < 0.05$) (Fig. 2).

The relationship between the serum level of sIL-2R and clinical data

In group A, the sIL-2R level was positively correlated with the urinary levels of protein and fibrin degradation products, the blood urea nitrogen level, and the serum level of creatinine and uric acid, and was negatively correlated with the glomerular filtration rate (Table 2). When the serum level of creatinine was above 2.0 mg/100 ml, the sIL-2R level were higher than cut-off value (Fig. 3).

In group B, the serum level of sIL-2R was positively correlated with the serum level of creatinine and negatively correlated with the glomerular filtration rate (Table 2).

Fig. 1. Serum levels of sIL-2R in patients without systemic diseases (Group A). sIL-2R, soluble interleukin 2 receptor; ANS, acute nephritic syndrome; RPNS, rapidly progressive nephritic syndrome; CNS, chronic nephritic syndrome; RH/PH, recurrent or persistent hematuria; NS, nephrotic syndrome
* $p < 0.05$ vs. the other 4 groups. (Bars) $\pm$ s.d.

Fig. 2. Serum levels of sIL-2R in patients with systemic diseases (Group B). sIL-2R, soluble interleukin 2 receptor; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SjS, Sjögren syndrome; PSS, progressive systemic sclerosis; MCTD, mixed connective tissue disease; DM, diabetes mellitus. (Bars) $\pm$ S.D. * $p < 0.05$

TABLE 2. Relationship between serum levels of sIL-2R and clinical data in patients with renal diseases

Parameter	Group A		Group B	
	<i>n</i>	Correlation coefficient	<i>n</i>	Correlation coefficient
U-TP	174	0.250***	68	0.106
U-FDP	25	0.895***	9	0.384
GFR	156	-0.432***	71	-0.240*
BUN	196	0.650***	83	0.155
S-CR	196	0.598***	83	0.293*
S-UA	195	0.377***	80	0.071

Group A, patients without systemic diseases; Group B, patients with systemic diseases; sIL-2R, soluble interleukin 2 receptor; U-TP, urine level of total protein; U-FDP, urine level of fibrinogen and fibrin degradation products; GFR, glomerular filtration rate; BUN, blood urea nitrogen; S-CR, serum creatinine; S-UA, serum uric acid.

* $p < 0.05$; *** $p < 0.001$

DISCUSSION

The serum level of sIL-2R is used to evaluate the stage of non-Hodgkin's malignant lymphoma (Pui et al. 1987) and adult T-cell leukemia (Nishimura et al. 1989). It has been reported that the serum level of sIL-2R is dependent on kidney function (Nassberge et al. 1992). The present study showed that the serum level of sIL-2R level was significantly higher in patients with renal diseases

Fig. 3. Correlation between the serum levels of sIL-2R and creatinine in patients without systemic diseases (Group A).

There was a positive correlation between the serum levels of sIL-2R and creatinine ($r=0.598$, $p<0.001$, $y=256.8x+281.5$), sIL-2R, soluble interleukin 2 receptor.

than in the control group and exceeded the upper limit of normal range in the acute nephritic syndrome and rapidly progressive nephritic syndrome groups. These data suggest that the serum levels of sIL-2R may increase in patients with renal disease, especially acute glomerular lesions.

Junghans and Waldmann (1996) reported that the increased serum levels of sIL-2R is due to the decreased excretion of sIL-2R in the presence of severe renal lesions. This study showed that the serum level of sIL-2R was positively correlated with the serum level of creatinine, and was negatively correlated with the glomerular filtration rate in patients with or without systemic diseases. These findings suggest that the serum levels of sIL-2R in patients with renal disease may correlate with the impaired renal function, and it may be a useful marker of renal function. Furthermore, we showed that the serum levels of sIL-2R were positively correlated with the degree of proteinuria in patients without systemic disease. These data suggest that in primary renal disease, the serum levels of sIL-2R may reflect the degree of renal damage.

In the present study, the serum level of sIL-2R was higher in the group with systemic diseases irrespective of the type of renal disease, than in the normal control group. However the correlation between parameters of renal function and sIL-2R levels were not as strong as observed in the group without systemic diseases. These data suggest that the increased sIL-2R levels in patients with systemic diseases may be dependent on the activity of systemic disease.

It has been reported that the serum level of sIL-2R is a marker of the activity of T-cell malignancies (Mackeen et al. 1986) and autoimmune disease (Wood et al. 1988). We showed that the serum level of sIL-2R was outside the normal range

in patients without systemic diseases with a serum level of creatinine above 2.0 mg/100 ml. The present findings suggest that the serum level of sIL-2R may be not useful indicator of diseases activity in patients with adult T-cell leukemia (ATL) or other autoimmune diseases when the serum level of creatinine was above 2.0 mg/100 ml.

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