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## CIRCULATING CYTOTOXIC ANTI-RCC ANTIBODY RESPONSES IN RENAL CELL CARCINOMA PATIENTS

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The circulating anti-RCC cytotoxic antibodies of eighteen RCC patients, preoperatively, and one inoperable case were studied by  $^{51}\text{Cr}$  release CDC and ADCC assays, using the cultured human RCC cell line, OUR-10. Circulating cytotoxic anti-RCC antibodies were detected in eight patients as CDC antibodies. The patients with a low pathological grade had a significantly higher percentage ( $P < 0.05$ ) of positive antibody responses.

**Key words:** Renal cell carcinoma, Cytotoxic antitumor antibody, Complement-dependent antibody, Lymphocyte-dependent antibody

### INTRODUCTION

The occurrence of spontaneous regression of pulmonary metastasis from renal cell carcinoma (RCC) is well documented, and the prognosis of RCC has been said to be influenced by the immunologic response of the tumor host<sup>1,2</sup>. Cell-mediated immunity<sup>3-8</sup> and humoral immunity<sup>6,9-13</sup> in RCC patients have been investigated extensively, and several investigators have demonstrated the existence of RCC-associated antigens.

Complement-dependent antibodies (CDA) have been demonstrated to be circulating cytotoxic anti-RCC antibodies only by the microlymphocytotoxicity assay, and not by the  $^{51}\text{Cr}$  release assay<sup>11,12</sup>. In addition to the CDA detected by its complement-dependent cytotoxicity (CDC), lymphocyte-dependent antibodies (LDA) can also be detected in the serum of RCC patients by antibody-dependent cell-mediated cytotoxicity

(ADCC) as in patients with other carcinomas<sup>14-19</sup>. On the other hand, the specificity of anti-tumor antibodies can be determined using normal autochthonous tissues. A cultured human renal cell carcinoma cell line was established from patient Y. Y. and designated as OUR-10<sup>20</sup>. In the present study, fresh peripheral lymphocytes could be obtained from this patient, who was still alive in a tumor-bearing state, and it was used to differentiate the anti-tumor antibody specificity from the histocompatibility antigens. In this paper, we studied whether the cytotoxic anti-RCC antibody against OUR-10 was present in the preoperative serum of RCC patients and what kind of cytotoxic anti-RCC antibodies were dominant in the preoperative state.

### MATERIALS AND METHODS

#### *Patients*

The circulating humoral cytotoxic res-

Table 1. Clinical data and circulating anti-tumor cytotoxic antibodies in the RCC patients

Case	Age	Sex	Histology			Tumor Weight	Prognosis		CDA			LDA		
			Cell type	Grade	Stage		Follow-up time(month)	OUR-10	RPMI 4788	PBL-YY	OUR-10	RPMI 4788	PBL-YY	
1 A.J.	65	M	Clear	II	P <sub>1</sub> NxMxV <sub>o</sub>	250 gm	49 mo.	Alive-NED	9.8 P<0.05*	5.4	3.4	11.3 P<0.01	-2.8	5.2
2 N.K.	60	M	Clear	II	P <sub>2</sub> NxMxV <sub>o</sub>	210	41	Alive-NED	9.7 P<0.05	1.1	5.2	2.8	-8.4	5.8
3 M.A.	60	M	Clear	II	P <sub>4</sub> NxM <sub>1</sub> cV <sub>o</sub>	250	8	Dead	20.9 P<0.01	5.8	3.7	4.0	-9.7	4.2
4 Y.K.	41	M	Clear	III	P <sub>4</sub> NxMxV <sub>o</sub>	650	12	Dead	22.1 P<0.02	7.6 P<0.2	-0.3	5.4	-1.3	1.8
5 I.Y.	51	M	Clear	II	P <sub>3</sub> NxMxV <sub>o</sub>	400	43	Alive-NED	10.6 P<0.05	-4.1	2.9	8.3 P<0.01	-10.0	5.5
6 A.S.	67	F	Dark	II	P <sub>2</sub> NxM <sub>1</sub> cV <sub>o</sub>	960	12	Dead	8.2 P<0.02	-1.4	ND	16.4 P<0.01	ND	3.5
7 M.S.	22	F	Dark	III	P <sub>2</sub> NxM <sub>1</sub> cV <sub>o</sub>	890	18	Dead	8.1 P<0.05	0.7	4.9	6.6	-3.2	4.9
8 K.Y.	74	M	Clear	II	P <sub>3</sub> NxMxV <sub>o</sub>	320	59	Alive-NED	7.6 P<0.02	-1.5	ND	4.9	-3.5	ND
9 I. I.	56	M	Clear	III	P <sub>2</sub> NxMxV <sub>1</sub>	800	21	Dead	6.6	0.7	4.3	7.7 P<0.2	-2.7	6.8
10 T.T.	62	M	Clear	II	P <sub>2</sub> NxMxV <sub>1</sub>	545	10	Dead	6.0	22.3 P<0.02	3.8	1.4	1.1	4.2
11 Y.Y.	32	F	Clear	II	P <sub>2</sub> N <sub>4</sub> M <sub>1</sub> bV <sub>o</sub>	650	16	Dead	5.0	11.5 P<0.02	6.6	6.5	-9.3	6.6
12 O.T.	39	M	Dark	III	T <sub>3</sub> NxMxVx	—	60	Dead	2.3	8.6 P<0.05	2.7	1.6	-8.5	5.8
13 E.M.	52	F	Clear	IV	P <sub>4</sub> NxMxV <sub>o</sub>	400	4	Dead	2.4	5.9	46.6 P<0.01	2.9	-17.6	8.3 P<0.01
14 F.K.	64	M	Mix	III	P <sub>3</sub> NxMxV <sub>o</sub>	800	29	Dead	3.9	-4.9	ND	7.3 P<0.2	-4.5	ND

15 N.M.	68 M	Clear	III	P <sub>2</sub> NxMxV <sub>0</sub>	370	40	Alive-NED	1.9	1.9	ND	4.0	-8.5	ND
16 Y.K.	40 M	Mix	IV	P <sub>2</sub> NxMxV <sub>0</sub>	205	13	Dead	4.0	-2.1	ND	3.6	-4.6	ND
17 K.H.	48 M	Clear	III	P <sub>4</sub> NxM <sub>0</sub> V <sub>0</sub>	1,050	13	Dead	3.3	2.5	ND	3.7	-5.2	ND
18 T.F.	69 M	Mix	IV	P <sub>3</sub> NxMxV <sub>0</sub>	725	8	Dead	0.1	ND	5.2	2.3	-8.5	1.3
19 M.H.	65 M	Clear	III	P <sub>3</sub> NxM <sub>1</sub> bV <sub>1</sub>	680	31	Dead	3.3	2.2	ND	3.8	-1.3	ND

NED: non-evidence of disease

\*: serum with more than 7,00% specific lysis and  $P < 0.05$  performed by Student t-test was considered to be positive

ND: not done

ponse to the RCC-associated antigen of nineteen RCC patients was studied using the cultured human RCC cell line designated as OUR-10<sup>20)</sup> (Table 1). The serum of the patients was drawn before nephrectomy in the eighteen operable cases or at the pathological diagnosis of renal carcinoma in one inoperable case, and stored at  $-70^{\circ}\text{C}$  until use. Follow-up studies of the nineteen cases were done at an interval of 3–5 years. Control serum of twelve, sex- and age-matched normal subjects were collected and stored at  $-70^{\circ}\text{C}$ . The patients were fifteen males and four females with a mean age of 54.5 years (range 22–74). Ten males and two females with a mean age of 52.6 years (range 16–80) served as the control group.

#### Target cells

As a RCC-associated antigen, the established cultured cell line, OUR-10 was used. The cultured human colon carcinoma cell line RPMI 4788 was used as a control cultured cell line. Since the RCC patient Y.Y., described in Table 1 and whose tumor was established as OUR-10, was still alive with residual tumor, freshly drawn peripheral mononuclear lymphocytes from this patient (PBL-Y.Y.) were used in this study as a control HLA-matched target cell. Cultured cell lines were maintained in RPMI 1640 supplemented with 20% fetal bovine serum (Microbiological Associates, Walkersville, Md.), 100 units of penicillin per ml, and 100 mg of streptomycin per ml (Medium A) in a humidified incubator containing 5%  $\text{CO}_2$ -95% air. Fresh PBL-Y.Y. were separated from Ficoll-Conray density gradient centrifugation and suspended in Medium A.

#### Cytotoxicity assay

In order to detect the humoral cytotoxic antibody activity,  $^{51}\text{Cr}$  release CDC and ADCC assay were employed. Two kinds of cultured cell lines, OUR-10 and RPMI 4788 were treated with 0.25% trypsin for 2 hrs at  $37^{\circ}\text{C}$ , and the cells were washed with Medium A thrice. Then, the cells were labeled with  $200 \mu\text{Ci Na}_2^{51}\text{CrO}_4$  for 2 hrs at  $37^{\circ}\text{C}$ , washed, and suspended in Medium A. Fresh PBL-Y.Y. was also

labeled with  $200 \mu\text{Ci Na}_2^{51}\text{CrO}_4$  by the same procedure. In the CDC assay,  $^{51}\text{Cr}$ -labeled target cells ( $1 \times 10^4$  cells in 0.05 ml) and heat-inactivated patient serum (0.05 ml) were mixed and incubated at  $37^\circ\text{C}$  for 30 min in a humidified 10%  $\text{CO}_2$ -90% air mixture incubator. Then 0.1 ml of unabsorbed rabbit serum (Behringwerke AG, Marburg, W Germany) was added as a complement to the mixture in triplicate for 2 hrs at  $37^\circ\text{C}$  in a flat-bottom microtest plate (Towakagaku, Tokyo, Japan). After a 2-hour incubation, the plate was centrifuged at 800 g for 10 min and the radioactivity of half of each supernatant was counted with a  $\gamma$ -counter (experimental release). Spontaneous release was obtained from the mixture containing target cells alone in the culture medium. Maximum release was calculated from the remaining half of the supernatant of the culture containing target cells in distilled water which was frozen and thawed in an acetone-dry ice bath thrice. Percent-specific lysis was calculated by the following formula:  $[(\text{experimental release} - \text{spontaneous release}) / (\text{maximum release} - \text{spontaneous release})] \times 100$ . Statistical significance was judged by the Student t-test between the group of replicates. In the CDC assay of fresh PBL,

the number of  $^{51}\text{Cr}$ -labeled target cells was  $2.5 \times 10^4$  cells in 0.05 ml culture medium.

In the ADCC assay, freshly drawn normal PBL was separated and used as the effector.  $^{51}\text{Cr}$ -labeled OUR-10 or RPMI 4788 ( $1 \times 10^4$  cells in 0.05 ml) or  $^{51}\text{Cr}$ -labeled fresh PBL-Y.Y. ( $2.5 \times 10^4$  cells in 0.05 ml) and heat-inactivated test serum (0.05 ml) were mixed and incubated for 30 min at  $37^\circ\text{C}$ . Then, effector PBL was added to the target cells at a ratio of 30:1, and the cultures in triplicate were incubated for 4 hrs at  $37^\circ\text{C}$  in flat-bottom microtest plates kept in a humidified 10%  $\text{CO}_2$ -90% air atmosphere. Spontaneous release was obtained from the mixture containing target cells alone in the culture medium. Percent-specific lysis was also calculated by the formula. Serum which showed more than 7% specific lysis with  $P < 0.05$  by the Student t-test was considered to be positive.

#### Staging

Renal cell carcinoma patients were classified into low or high stage, based on Robson's criteria (21). The group of patients with stage  $\text{P}_3$  cancer without metastasis or venous thrombus, were regarded as low stage.

#### Grading

Histological cell type was divided into

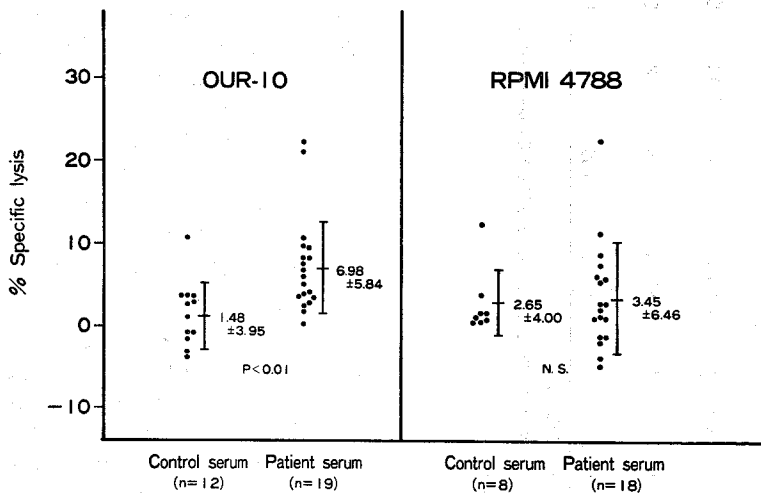


Fig. 1. A comparison of CDC activity to OUR-10 and RPMI 4788 of RCC patient serum and age and sex matched control serum. Percent specific lysis was calculated by the formula described in the text. Statistical analysis was performed by Student t-test

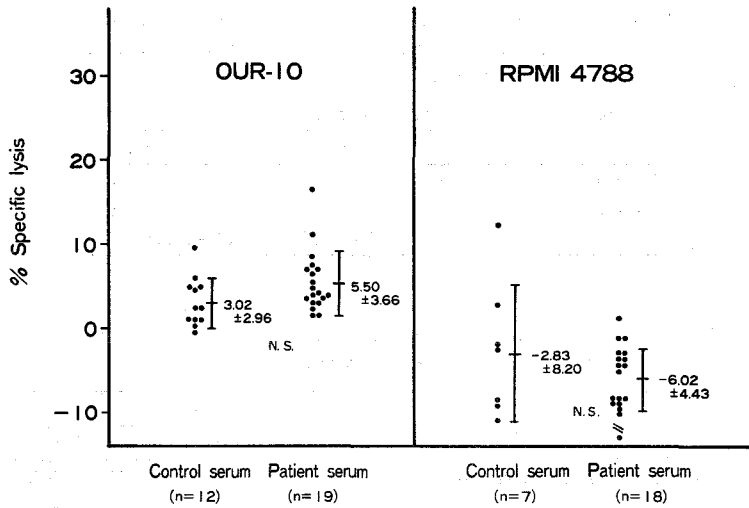


Fig. 2. A comparison of ADCC activity to OUR-10 and RPMI 4788 of RCC patient serum and age and sex matched control serum. Spontaneous release of each target cells of OUR-10 and RPMI 4788 (SR/MR  $\times$  100) was  $25.96 \pm 4.25$  and  $27.70 \pm 1.69$  respectively. Natural killer activity against each OUR-10 and RPMI 4788 cell lines showed  $1.69 \pm 2.65$  and  $18.08 \pm 7.32$  of per cent specific lysis respectively

clear, dark or mixed type by the criteria of Claes<sup>22</sup>). Pathological grading was also divided into four groups, based on the criteria of Skinner<sup>23</sup>). Low grade patients had either grade I and II cancer.

## RESULTS

### *Anti-RCC cytotoxic antibodies*

Circulating anti-RCC cytotoxic antibodies having CDC and ADCC activity against OUR-10 were studied, and Table 1 shows the results.

Fig. 1 shows the CDC activity of the sera of the patients and healthy control group against OUR-10, and RPMI 4788. The patients with RCC had a higher CDC activity against only OUR-10 (mean percent specific lysis  $6.98 \pm 5.84$ ) which was statistically significant ( $P < 0.01$ ) compared with the control group. Neither the patient nor control group showed a high CDC activity against RPMI 4788. As shown in Table 1, eight RCC patients showed positive CDC activity against OUR-10 and none of them had CDC activity against either RPMI 4788 or PBL-Y.Y. On the other hand, one of the control serum showed positive CDC activity against OUR-10, but it also reacted

with PBL-Y.Y. Therefore, it was considered to contain an alloantibody, such as anti-HLA antibody.

Before analysing the ADCC activity of tested sera using cultured cell lines as target it is necessary to know whether these cell lines are susceptible to allogenic natural killer (NK) cell activity. In the present study, human fresh PBL was found to show NK cell activity not to OUR-10 (mean percent specific lysis  $1.69 \pm 2.65$ ) but to RPMI 4788 (mean percent specific lysis  $18.08 \pm 7.32$ ). Therefore, the spontaneous release in the ADCC assay to RPMI 4788 cell line might be the effect of NK cell activity. Fig. 2 shows the mean ADCC activity of both patient and normal control group sera against OUR-10, RPMI 4788 and PBL-Y.Y. The ADCC activity to OUR-10 of the patients was not significantly higher than that of the control subjects. Only three patients in the RCC group showed positive ADCC activity against OUR-10, and these positive sera also had CDC activity against OUR-10. In the present study, there were not RCC patient sera which showed only ADCC activity against OUR-10. The above results in-

Table 2. A correlation between the presence of anti-RCC cytotoxic antibodies and pathological grading or clinical staging

Anti-RCC cytotoxic antibodies	Pathological grading		Clinical staging	
	Low	High	Low	High
Positive	6	2	4	4
Negative	2	9	4	6
	X <sup>2</sup> =4.02 P<0.05		X <sup>2</sup> =0.003 NS	

Table 3. A correlation between the presence of anti-RCC cytotoxic antibodies and patient survival rate

	Actuarial patient survival rate				
	1 yr	2yrs	3yrs	4yrs	5yrs
The present nineteen cases (n=19)	0.6842 (19)	0.4210 (13)	0.3158 (9)	0.3158 (7)	0.1578 (4)
Antibody positive (n=8)	0.6250 (8)	0.5000 (5)	0.5000 (4)	0.5000 (4)	0.5000 (2)
Antibody negative (n=11)	0.7271 (11)	0.4545 (8)	0.2727 (5)	0.2727 (3)	0.1364 (2)
Overall cases * (n=116)	0.7272 (116)	0.5656 (74)	0.4589 (54)	0.4099 (42)	0.3468 (33)

\* One-hundred sixteen RCC patients including the present 19 cases were observed between Jan. 1957 and Dec. 1980.

dicade that in the preoperative RCC patients, cytotoxic anti-RCC antibodies did exist and that CDC antibody production in the circulating humoral immunity against OUR-10 which may be associated with RCC antigen, is preponderant over ADCC antibody production.

*Correlation between the presence of cytotoxic anti-RCC antibodies and pathological grading, clinical staging or patient survival*

As seen in Table 2, low grade RCC patients showed a significantly high incidence of cytotoxic anti-RCC antibodies during the preoperative state ( $P<0.05$ ), but no significant correlation between antibody response and clinical staging was found. Concerning patient survival, the antibody-positive group had a better patient survival rate than the antibody-negative group, but statistical analysis was not performed. When survival rate of antibody positive patients was compared with that of a larger number of RCC patients ( $n=116$ ) including the present nineteen cases, the survival rate of the present antibody positive group at five years was only slightly higher (Table 3).

## DISCUSSION

The present studies showed that eight out of nineteen RCC patients had cytotoxic anti-RCC antibodies during the preoperative state, and that the production of cytotoxic anti-RCC antibodies of CDC is dominant over that of ADCC in type specificity. Previous reports concerning anti-RCC humoral antibody<sup>11,12</sup>, did not elucidate what sort of cytotoxic antibodies, that is CDA or LDA, were produced in the serum of RCC patients. Its clarification, would enable speculation of the kind of humoral immunity, CDC or ADCC mechanism important in destruction of RCC tumor cells in vivo, and a tumor-associated antigen expressed on a cultured cell line could be detected by either CDC or ADCC assay, since it has been reported that a difference in the nature of the antigen or the amount of antigen expressed on target cell surface is known to induce either CDC or ADCC in humoral antibody response<sup>18</sup>. For example, Hahn<sup>19</sup> showed that a colon cancer-associated antigen which was exp-

ressed on a cultured cell line of RPMI 4788 could be detected mainly by ADCC but not by CDC assay. Therefore, it is implied that an RCC-associated antigen expressed on a cultured cell line of OUR-10 could be detected mainly by CDC rather than ADCC assay, since the incidence of CDC antibody activity was high in the RCC patients (Table 1). However, further study using several kinds of RCC cultured cell lines as target will be necessary to clarify what kind of humoral anti-tumor cytotoxic immunity is dominant in the RCC patients.

Antibody specificity found in the RCC patient serum was considered to be against a RCC-associated antigen, since positive serum against OUR-10 did not react with PBL-Y.Y. which shared the same histocompatibility antigens as the cultured cell line of OUR-10 and they did not react with another PBL too.

Anti-tumor immunity was present, in general, in the case of small tumor burdens and usually absent and not detectable in patients with widespread metastasis<sup>24-27</sup>. On the other hand, few studies have been made on the correlation between the presence of anti-tumor humoral antibody and the pathological grading. O'Boyle, however, showed that anti-tumor cell-mediated and humoral immunity was present in low grade bladder carcinoma patients<sup>28</sup>. In our study, the presence of anti-tumor antibody against RCC-associated antigens was well correlated with low pathological grading, but not with low clinical staging (Table 2). Though it is not well known why most of the high grade RCC patients could not produce anti-RCC antibody against such an antigen as OUR-10, several speculations can be made: (1) High grade tumors might have a low concentration of tumor-associated antigens on the cell surface. On the other hand, low grade tumors might have a high concentration of tumor antigens, because in Moloney virus tumor system, a tumor with a high concentration of surface antigens is known to be highly susceptible to the cytotoxic reaction *in vitro* and *in vivo*, while tumors with a low concentration are resistant<sup>29</sup>. Or, high grade tumor might

have a very high concentration of tumor-associated antigens to lead to the high dose tolerance in the host. (2) A tumor-associated antigen of high grade tumor would induce the suppressor cell and fail to produce the anti-tumor antibody. Our findings that six out of eight low grade RCC patients had anti-RCC antibodies might support the first speculation, because if the two low grade RCC tumor T.T. and Y.Y., with negative anti-tumor antibody, had a larger amount of tumor-associated antigen, they might fail to elicit the anti-tumor antibody production due to high dose tolerance. However, further study to elucidate the relations between the tumor-associated antigen on the cell surface and the pathological grading of human tumor will be necessary to confirm the first speculation.

Our present study also demonstrated that anti-RCC antibody positive patients survived longer than antibody negative patients (Table 3). On the other hand, we did not elucidate the relationship between the presence of cell-mediated cytotoxicity (CMC) to OUR-10 and RCC patient survival, or the effect of humoral antibody on the CMC to OUR-10, since the lymphocytes of the present patients could not be stored. However, we studied whether CMC activity of the lymphocytes of another RCC patient in a preoperative state is present against OUR-10 performed by <sup>51</sup>Cr release assay; no CMC activity of patient lymphocytes could be found in all cases (unpublished data). It is likely that the killer lymphocytes of the RCC patient were blocked by soluble tumor antigens or other blocking factors<sup>30,31</sup>. Therefore, our present findings are taken to imply that humoral immunity rather than cellular immunity against an RCC-associated antigen is present in the preoperative state of RCC patients. And, it would be likely that humoral cytotoxic antibody response, mainly by CDC mechanism rather than ADCC mechanism, plays a role in the RCC tumor destruction *in vivo*.

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## 和文抄録

## 腎細胞癌患者血清中の抗腫瘍抗体について

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渡辺信一郎

腎細胞癌患者19症例の血清について、ヒト腎細胞癌培養株 OUR-10 に対する抗腫瘍抗体を  $^{51}\text{Cr}$  release 法による complement-dependent cytotoxicity (CDC) と antibody-dependent cell-mediated cytotoxicity (ADCC) の各 assay で検討した。19症例のうち8症例 (42.1%) に抗 RCC 抗体が認められ、

OUR-10 に対する殺細胞性抗体は補体依存性抗体として同定された。抗 RCC 抗体陽性患者について、病理学的 grade と臨床的 stage との相関をみると、low grade 症例に陽性率が有意に高く ( $P < 0.05$ )、stage との関係はみられなかった。