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Cell surface expression and serum levels of intercellular adhesion molecule-1 in renal cell carcinoma

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Abstract Intercellular adhesion molecule-1 (ICAM-1) is the natural ligand of the T-lymphocyte adhesion molecule LFA-1 (lymphocyte-function-associated antigen-1). ICAM-1 is involed in target cell recognition by T-lymphocytes, LAK cells and natural killer cells. The molecule has also been detected on a variety of normal cells and on human tumors. Renal cell carcinoma (RCC) is one of the few tumors that respond to immunotherapy, but clinical results are generally disappointing. We therefore analyzed, by immunohistochemistry, the expression of ICAM-1 in pairs of normal kidneys, RCC, and RCC metastases. Moreover, serum ICAM-1 was determined in RCC patients and compared with surface expression of cell-bound ICAM-1. Strong glomerular expression of ICAM-1 was observed in all specimens of normal kidney examined. Proximal tubuli were weakly stained in the majority of specimens. Of the tumors, 80% stained positive for ICAM-1. Although ICAM-1 was detected on the majority of extrarenal tumor specimens examined, staining was generally weaker in the metastases. Patients without metastases at initial presentation more frequently expressed ICAM-1 in their primary tumors than did patients with metastases. Levels of serum ICAM-1 (sICAM-1) were significantly higher in RCC patients than in controls with non-malignant renal diseases. Patients with an unfavorable prognosis, e.g. with advanced tumor stage or metastasis at initial presentation, had higher levels of sICAM-1 than patients with low-grade and/or low-stage tumors. An inverse correlation was observed between expression of ICAM-1 in tumors and levels of sICAM-1. On the basis of our data we suggest that cell-bound or soluble ICAM-1 is correlated with tumor-host interaction in RCC.

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Renal cell carcinoma (RCC) is one of few tumor types that respond to immunotherapy (for review see [18]). Although tumor-infiltrating lymphocytes (TIL) are found in significant numbers in the majority of tumors and may be activated for destruction of tumor cells in vitro [15], response rates of adoptive therapy with TIL or LAK are generally disappointing. It is therefore of importance to analyse the molecular factors involved in target recognition by cytotoxic lymphocytes.

Intercellular adhesion molecule-1 (ICAM-1) is closely associated with target recognition of cytotoxic T-lymphocytes, LAK cells or monocytes [2, 7, 22, 37]. ICAM-1 is a glycoprotein molecule that is sialylated in a tissue-specific manner [31]. Structurally, ICAM-1 is a member of the "immunoglobulin superfamily" and is therefore related to MHC class I and II, the T-cell receptor for antigen, N-CAM, CEA and others (for review see [20]). ICAM-1 is expressed on B-lymphocytes, monocytes, NK (natural killer) cells, vascular endothelium, fibroblasts and other cells. The molecule serves as a ligand for lymphocyte functional antigen-1 (LFA-1) [27], which is expressed on T- and B-lymphocytes, NK cells, granulocytes and macrophages [11]. ICAM-1 can be induced in vitro on vascular endothelium by pre-inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor (TNF) or γ-interferon (IFN-γ). ICAM-1 is not only found in inflammation, but has also been detected on tumors such as neuroblastoma [14], brain tumors [16], melanoma [20, 34], lymphoma [37] and thyroid carcinoma [4]. In melanoma, presence of ICAM-1 has been associated with an unfavorable prognosis [20].

A soluble variant of ICAM-1 has been identified in several inflammatory diseases and some tumors such as melanomas and gastrointestinal tumors [23, 28, 36]. The origin and physiology of sICAM-1 is not completely understood at present.

In an attempt to achieve better definition of the association of ICAM-1 in progression and tumor-host interaction of RCC, we analyzed the expression of ICAM-1 on normal kidney, primary tumors, metastases and in the serum of patients with RCC.

Materials and methods

Patients

Of the 44 patients examined in this study, 28 were male, and 16 were female. Average age was 62.2 years, with a range of 32–83 years. In all patients, tumor stage, grade of malignancy and lymph node infiltration were determined by pathohistological examination. M stage was determined by chest X-ray and CT scan. T stage was T1 in 7 patients, T2 in 18 patients and T3 in 10 patients. In 6 patients, macroscopic invasion of renal vein or vena cava was observed (T3b). Grade of malignancy was G1 in 7 patients, G2 in 31 patients and G3 in 5 patients. Lymph nodes were free of disease in 36 patients, while 5 patients had N1 and 3 patients, N2 nodes. The patients included 37 who were clinically free of metastasis at initial presentation. In 7 patients, extrarenal tumor had been detected before surgery: 3 of these had metastases restricted to the lungs, 1 had metastases in lungs and brain, 2 patients had bone metastases and 1 patient had pleuritis carcinomatosa.

In 33 patients, normal renal tissue and renal tumor tissue were examined in parallel; in 5 patients, additional specimens from extrarenal tumor were available (lymph node metastases, distant metastases, thrombus of vena cava). For 3 patients, specimens were available from metastases but not from the primary tumor.

Serum levels of ICAM-1 were determined in 50 patients, 30 of whom had histologically confirmed RCC. Normal renal tissue and renal cell carcinoma was available for immunohistochemistry in 24 of these patients; in 4 patients, a metastatic lesion was examined by immunohistochemistry in parallel to serological evaluation.

Sera of 20 non-RCC patients served as controls for sICAM-1 determination: 10 were obtained from patients with untreated urolithiasis, while 10 sera were from patients with untreated IgA-type glomerulonephritis and were kindly provided by Dr. P. Heering (Department of Nephrology, Heinrich-Heine-Universität Düsseldorf).

Materials

Monoclonal antibody with specifity for ICAM-1 and anti-mouse antibody were from Dianova (Hamburg, Germany); mouse peroxidase-antiperoxidase (PAP) complex was from DAKO (Glostrup, Denmark). Fetal bovine serum (FBS) was obtained from Biochrom/Seromed (Berlin, Germany). All plastic culture dishes were obtained from Nunc (Roskilde, Denmark). If not specifically indicated, all other chemicals were from Sigma (Munich, Germany).

Methods

Immunohistochemistry

Surgical specimens from RCC and from normal renal tissue of the contralateral edges of the kidneys involved were snap-frozen in isopentane at −125°C and kept frozen at −70°C prior to use. Immediately before immunohistochemistry tissue was cut in 5 µm sections on a Leitz cryostat, mounted on slides and fixed with ethanol/methanol (1:1) for 10 min at room temperature.

Staining of the sections was performed by means of the peroxidase-anti peroxidase technique of Mason et al. (1982). In order to inhibit non-specific binding of proteins, frozen sections were incubated with 3% bovine serum albumin (BSA) for 20 min at room temperature. Then, the primary antibody, clone 84H10, which was directed against CD54 (ICAM-1), was added at a dilution of 1:40 in PBS for 30 min at room temperature. After three washes with PBS, a non-labelled anti-mouse "bridge" antibody was added at a dilution of 1:25 for 30 min at room temperature. After another three washes with PBS, bound antibody was detected with a mouse peroxidase-anti-peroxidase (PAP) complex that was applied to the sections for 30 min at room temperature, followed by three washes with PBS. Diaminobenzidine (DAB) was used as a substrate for peroxidase; nickel chloride was used for amplification of staining. A substrate solution consisting of 6 mg of 3.3 diaminobenzidine in 9 ml of 50 mM Tris buffer, 1 ml of 0.3% (w/v) nickel chloride in Tris buffer and 10 µl 30% H_2O_2 was added to the sections for 15 min at room temperature with avoidance of light exposure. After termination of incubation, sections were thoroughly washed in distilled water, counter-stained in Mayer's hemalaun for 3 s, and washed in distilled water twice for 5 min. Sections were then dehydrated in increasing concentrations of alcohol and mounted in Depex.

Intensity of staining was arbitrarily classified as follows:

++ significant staining of the majority of cells
+ significant staining of large areas of the section
(+) weak, but significant staining
− no staining

Evaluation of stained sections was performed by two independent observers.

Enzyme-linked immunoassay for determination of serum ICAM-1

Serum levels of ICAM-1 (sICAM-1) were determined with a commercially available sandwich-ELISA (enzyme-linked immunoassay) kit (Bender MedSystems, Vienna, Austria) exactly as recommended by the manufacturer. Briefly, tissue culture plates were supplied coated with a "catching antibody" to ICAM-1. For detection of bound sICAM-1, a horseradish-peroxidase-labelled antibody was added. After incubation for 2 h at room temperature, unbound material was washed off the plate. For detection, tetramethylbenzidine (TMB) was added as a substrate for 15 min at room temperature. Reaction was stopped by addition of 4 *N* sulfuric acid, and the colored substrate was measured at 450 nm in an ELISA reader (EAR 400 AT, SLT Labinstruments, Gröding/Salzburg, Austria). Results were expressed as optical density (OD). ICAM-1 concentration was computed from OD by calculation of a standard curve from ICAM-1 standards supplied by the manufacturer.

Statistical analysis

Immunohistochemical detection of ICAM-1 was correlated to clinical parameters such as TNM staging by using McNemar's modified sign test.

Serum concentrations of ICAM-1 in patients with RCC, patients with glomerulonephritis, and patients with urolithiasis were compared by means of the Mann-Whitney-Wilcoxon test. Test value U was calculated by computing the ranks of the serum concentration in the two groups compared. The null hypothesis was that the values of two groups were equal ($H_0: P(X_1 > X_2) = 0.5$). The null hypothesis was rejected and the alternative hypothesis ($H_A: P(X_1 > X_2) = 0.5$) accepted if the test value U was smaller than the critical values looked up in the table of probability for the Mann-Whitney-Wilcoxon test.

Correlation of tissue expression and serum levels of ICAM-1 was evaluated by calculating the coefficient of contingency according to Pearson [24]. Complete contingency would be assumed if all patients with a serum concentration above a critical value were positive for tissue expression of ICAM-1.

Table. 1 Expression of intercellular adhesion molecule-1 (ICAM-1) in renal cell carcinoma (RCC) in relation to tumor stage, tumor grade and histology

	n	Percent of sections positive
All patients	30/38	79
T1	4/5	80
T2	14/16	88
T3	14/17	83
G1	4/5	67
G2	25/28	86
G3	3/5	60
N0	26/30	87
N1	4/5	80
N2	2/3	67
M0	28/32	87
M1	4/6	67
Clear cell carcinoma	24/28	86
Papillary carcinoma	3/3	100
Chromophilic carcinoma	1/2	50
Chromophobic carcinoma	3/4	75

Results

Immunohistochemistry of ICAM-1 in normal kidney

Expression of ICAM-1 in normal kidney was examined in 38 patients. Normal kidney was obtained from patients undergoing tumor nephrectomy. The specimens were taken from an area of the kidney that was located as far distant as possible from the tumor. The absence of tumor in the specimens was confirmed by histological examination after HE staining.

ICAM-1 was detected in all specimens of normal kidney. Staining intensity was intermediate ("+") in all specimens. All glomeruli stained positive for ICAM-1 (Fig. 1). Moreover, weak but significant staining was observed in the proximal tubuli. This shows that ICAM-1 is present in specific locations of normal kidney.

Immunohistochemistry of ICAM-1 in renal cell carcinoma

Thirty-eight RCC specimens were analyzed for expression of ICAM-1. The presence of malignant tumor was confirmed by histological examination of HE-stained tissue. In 30 out of 38 patients (79%), the presence of ICAM-1 could be detected on immunohistochemical examination of the tumors. Staining was strong (++) in 10/30, intermediate in 15/38, and weak in 5/38 specimens. ICAM-1 was not uniformly but focally distributed (Fig. 2). Areas of connective tissue, such as intratumoral septa, never stained positive for ICAM-1.

We then compared ICAM-1 expression with tumor stage, tumor grade and tumor histology (Table 1). Of 28 clear cell carcinomas, 24 stained positive for ICAM-1. All papillary tumors examined expressed ICAM-1. The rate of ICAM-1-positive tumors decreased with increasing N stage. (N0: 87%, N1: 80%, N2: 67%). No such correlation was observed with differing tumor grade. Numbers in subgroups were, however, too low to reach statistical significance.

In the patients who initially presented with distant metastases 67% of the primary tumors were positive for ICAM-1, whereas among the patients who were clinically free of metastases before surgery, 88% of the primaries stained positive for ICAM-1.

It has been suggested in the literature that expression of ICAM is enhanced in areas of leukocytic infiltration. We therefore incubated some tumor specimens with CD45, a panleukocytic marker, in parallel to ICAM-1 determination. CD 45-positive leukocytes were detected in RCC specimens. We failed, however, to demonstrate a clear correlation between leukocytic infiltration and ICAM-1 expression (data not shown).

Immunohistochemistry of ICAM-1 in RCC metastases

Eight specimens of extrarenal RCC were examined in our study. Sources of extrarenal tumor were skin ($n=2$), bone ($n=1$), lymph node ($n=3$) and thrombi of vena cava ($n=2$).

In all lymph node metastases examined, a significant, almost uniform, expression of ICAM-1 was observed (Fig. 3). Of the two cava vein thrombi examined, one was moderately stained, whereas no ICAM-1 could be demonstrated in the other thrombus (Fig. 3). The two skin metastases examined were either negative or only weakly positive for ICAM-1. In a bone metastasis derived from cervical spine, staining was focally distributed (Fig. 3).

In 5 patients, ICAM-1 expression in the primary tumor and a metastasis was compared. In 4 out of 5 specimens, ICAM-1 expression was weaker in the metastasis than in the primary tumor.

Serum ICAM-1 in RCC

Serum levels of ICAM-1 were determined in 50 patients, 30 of whom had histologically proven RCC, while 10 patients with untreated IgA glomerulonephritis and 10 patients with untreated urolithiasis served as controls (Fig. 4). In 29/30 patients with RCC (Table 2), SICAM-1 levels were above the normal range, which was – according to information provided by the test kit manufacturer – between 129.9 and 297.4 ng/ml. Mean was 520.88 ng/ml, with a range of 289–759 ng/ml and a standard deviation of 114.90 ng/ml.

Among the 10 patients with untreated acute IgA glomerulonephritis, sICAM-1 levels were in the upper normal range in 3/10 and above normal in 7/10. The mean for the glomerulonephritis controls was 427.5 ng/ml, with a range of 282–604 ng/ml and a standard deviation of 129 ng/ml. The mean serum concentration in RCC pa-

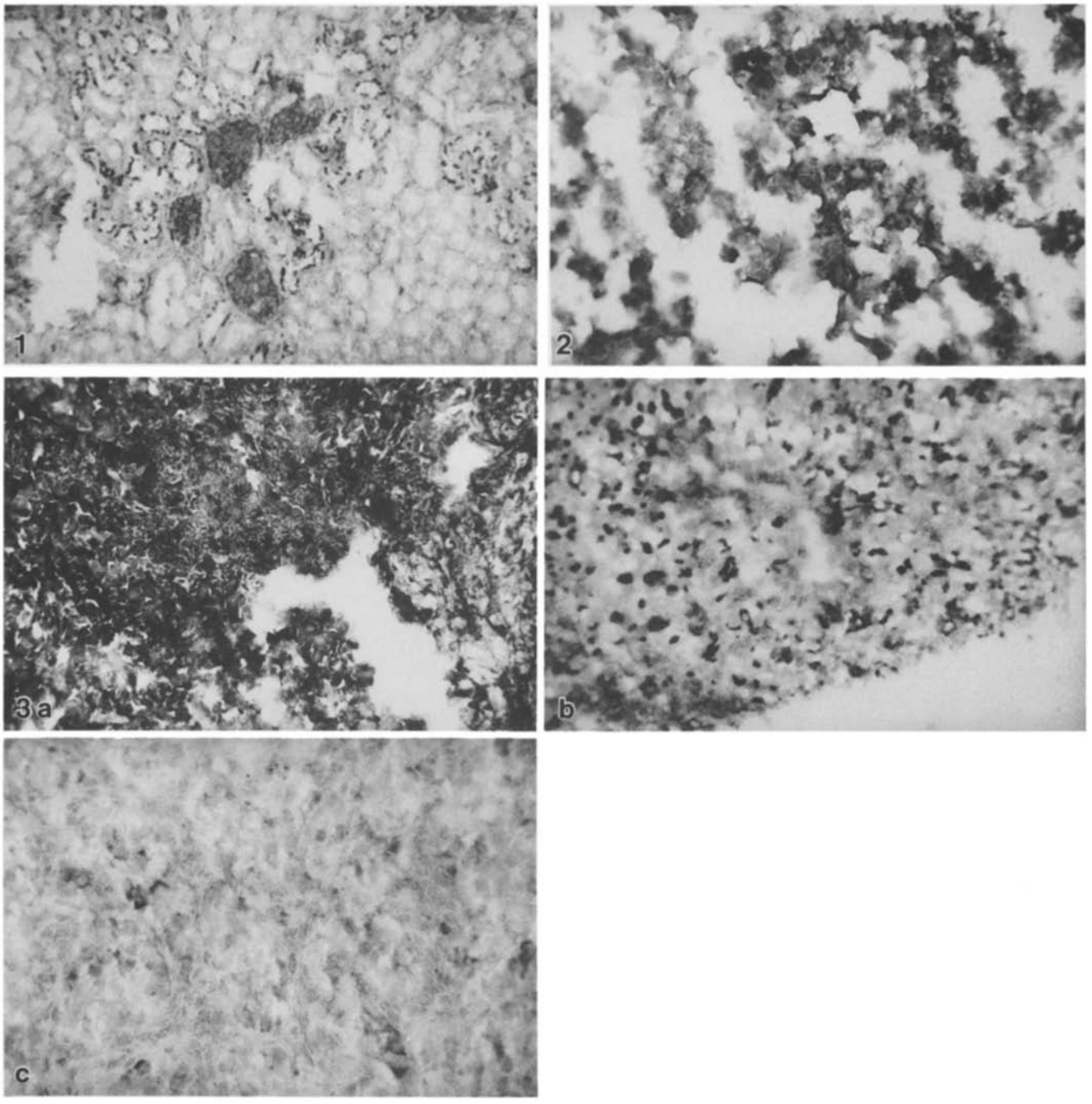

Fig. 1 Expression of intercellular adhesion molecule-1 (ICAM-1) on frozen section of normal kidney. ×40

Fig. 2 Expression of ICAM-1 on frozen section of renal cell carcinoma (RCC). ×100

Fig. 3A–C Expression of ICAM-1 on frozen sections of extrarenal tumor. **A** Lymph node metastasis; **B** thrombus in vena cava; **C** bone metastasis. ×100

tients was significantly higher than that in patients with glomerulonephritis ($P \leq 0.01$).

In all patients with untreated urolithiasis, ICAM-1 was above normal. Lowest serum concentration was 25% above the upper normal range (297.4 ng/ml). The mean ICAM-1 level was 484 ng/ml, with a range of 378–678 ng/ml and a standard deviation of 103 ng/ml. Mean ICAM-1 concentration was 36 ng/ml higher in RCC patients than in patients with urolithiasis. The Mann-Whitney-Wilcoxon test revealed a significant difference between the groups ($P \leq 0.25$).

It has been reported in the literature that sICAM-1 are an important prognostic factor in malignant melanoma. Therefore, serum concentrations of ICAM-1 were compared with tumor stage and grade (Table 3). With increasing tumor stage, serum levels of ICAM-1 were found to be elevated in patients with RCC (T1: 483 ng/ml, T2: 522 ng/

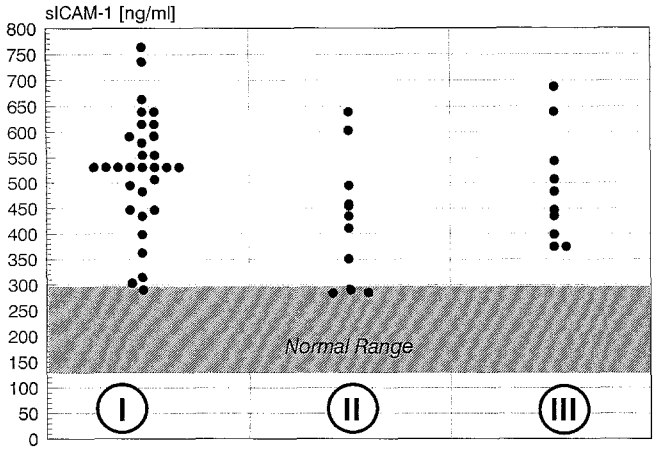

Fig. 4 Serum concentrations of ICAM-1 in patients with RCC (*I*), acute glomerulonephritis (*II*), and urolithiasis (*III*). Normal range is between 129.9 and 297.4 ng/ml, according to information provided by the manufacturer of the test kit

Table 2 Serum concentration of ICAM-1 in patients with RCC

	Serum ICAM-1 concentration	*n*
All patients	520.88 ng/ml	30
T1	438.72 ng/ml	5
T2	522.68 ng/ml	11
T3	532.73 ng/ml	14
T3a	497.09 ng/ml	11
T3b	662.77 ng/ml	3
G1	501.68 ng/ml	6
G2	527.91 ng/ml	23
G3	444.20 ng/ml	1
N0	526.00 ng/ml	27
N1	474.13 ng/ml	3
N2	0	0
M0	508.64 ng/ml	27
M1	631.03 ng/ml	3
Cell surface ICAM-1 positive	500.11 ng/ml	20
Cell surface ICAM-1 negative	586.21 ng/ml	5
Clear cell carcinoma	532.73 ng/ml	14
Papillary carcinoma	444.20 ng/ml	1
Chromophilic carcinoma	300 ng/ml	1
Chromophobic carcinoma	558.67 ng/ml	3

Table 3 Serum concentrations of ICAM-1 in relation to tumor stage and grade of malignancy

	200–400 ng/ml	401–600 ng/ml	>600 ng/ml
T1	1	4	0
T2	2	6	3
T3	3	8	4
N0	5	17	6
N1	1	1	1
N2	0	0	0
M0	6	17	0
M1	0	1	2
G1	1	5	0
G2	5	12	7
G3	0	1	0
	$n=6$	$n=18$	$n=7$

ml, T3: 532 ng/ml). Serum ICAM-1 was higher in T2 tumors than in T1 tumors ($P \leq 0.1$). Differences in sICAM levels between T2 and T3 tumors did not reach statistical significance.

Patients with involvement of renal and/or caval vein had significantly higher levels of sICAM-1 (662 ng/ml, $P \leq 0.025$) than patients with all other tumor stages, including T3a. Serum levels of patients with distant metastases at first presentation were significantly higher than levels of patients without distant metastases (631.03 ng/ml vs 508.64 ng/ml). Tumor grading or lymph node involvement did not seem to have an influence on sICAM-1 levels.

All patients with T1 tumors had serum levels below 600 ng/ml. Moreover, no patient with G1 tumors had serum levels above 600 ng/ml. In patients at low risk of tumor progression, then, sICAM-1 levels never exceeded 600 ng/ml. In contrast, all patients with a high risk of tumor progression had serum levels above 500 ng/ml.

Correlation of sICAM-1 with expression of ICAM-1 in RCC tissue

In 26 patients, RCC tissue specimens and serum for determination of sICAM-1 were available at the same time (Table 3). In patients without ICAM-1 expression in frozen sections of the primary tumor, sICAM levels were higher than in patients with tumor sections positive for ICAM-1. The difference was significant at $P \leq 0.1$. Thus, sICAM-1 levels seem to be inversely correlated with ICAM-1 expression in the tumor.

Discussion

ICAM-1 is the natural ligand of the β2 integrins LFA-1 [30] and Mac-1 [9]. Both ICAM-1 and LFA-1 are found on leukocytes. ICAM-1 can also be demonstrated on cells other than white blood cells, such as liver, adrenals, thymus and vascular endothelium [29]. Expression of ICAM-1 on vascular endothelium may be enhanced up to 40-fold by addition of cytokines, e.g. IL-1, TNF, and IFN-γ [11]. LFA-1-positive leukocytes may bind to activated endothelium expressing ICAM-1 before they invade inflamed tissue. An adhesive contact between complementary cells is induced by interaction of ICAM-1 with its ligands. Addition of antibody to ICAM-1 may inhibit immune responses in vitro, such as mixed lymphocyte reaction [6], cell-mediated cytotoxicity [33], lymphokine-activated killing [2] or antigen-induced lymphocyte proliferation [10]. Target cell contact of leukocytes does not, however, seem to be mediated by ICAM-1/LFA-1 exclusively [11, 26].

ICAM-1 has been detected on normal kidney by us and others [13, 21]. Glomeruli, and few proximal tubuli were the predominant locations of ICAM-1 expression in normal kidney. The function of ICAM-1 in normal kidney

is not known at present. In renal inflammation, such as glomerulonephritis or transplant rejection, distinct changes in ICAM-1 expression have been described. Increased glomerular expression of ICAM-1 in glomerulonephritis or de novo expression of ICAM-1 in renal tubuli in transplant rejection may be indicators for an increased attraction of leukocytes to the respective structures. In fact, Bishop and Hall [5] have been able to demonstrate that activated T-lymphocytes bind to ICAM-1-positive tubuli in vitro. In their experiments, adhesion of activated T-lymphocytes to tubulus cells could be inhibited by addition antibodies to either ICAM-1 or LFA-1. It is therefore likely that expression of ICAM-1 is an early step in immune reactions in the kidney. In vivo experiments with antibody to ICAM-1 as therapy for acute transplant rejection have been reported [8].

In our experience, ICAM-1 expression was detected in the majority of tumor specimens tested. Immunohistochemical staining was not uniform but focal; areas with connective tissue never stained positive for ICAM-1. Results reported by Tomita et al. were thus confirmed [35]. ICAM-1 expression is not an specific feature of RCC; it has been found in a variety of lymphoid and solid tumors, such as neuroblastoma [14], brain tumors [16], melanoma [20], lymphoid tumors [38] and thyroid cancer [4]. Tomita et al. [35] showed a positive correlation of ICAM-1 expression with mononuclear cell infiltrate of the respective tumors. In the present study, mononuclear cell infiltrate was not found to be strictly correlated with ICAM-1 expression in the few sections that were stained for ICAM-1 and a pan-leukocyte marker in parallel.

In malignant melanoma, expression of ICAM-1 on tumors was found to be correlated with an unfavorable prognosis [20]. This finding has been explained by the hypothesis that binding of lymphocytes to melanoma cells in situ would interfere with homotypic aggregation of tumor cells and thus enable tumor cells to detach from the primary tumor.

In our exprience, ICAM-1 expression was less frequent in patients with metastases at initial presentation than in those without metastases. Moreover, frequency of ICAM-1 expression decreased with increasing lymph node involvement. Metastases were less frequently positive for ICAM-1 than primary tumors. Thus, in our patients, lack of ICAM-1 expression was correlated with a less favorable prognosis. In acute inflammation, it has been shown that T-lymphocyte activity is critically dependent on binding to ICAM-1-positive tubulus cells. If the same principle is applied to renal tumors, it should not be surprising that patients with high expression of ICAM-1 have a more favorable prognosis.

ICAM-1 has been detected not only bound to cell membranes but also in the serum of patients with inflammatory diseases [28]. Three isoforms have been described that are structurally different from cell-bound ICAM-1. In our study, sICAM-1 was determined in 50 patients, 30 with histologically proven RCC, 10 with acute untreated IgA glomerulonephritis and 10 with untreated urolithiasis. Serum levels in patients with RCC were significantly higher than those in controls. In the presence of involvement of the renal and/or caval veins, sICAM-1 levels were significantly elevated compared with stages without vascular involvement. Correlation of sICAM-1 with tumor stage did not reach levels of significance; however, no patients with T1 and/or G1 tumor had serum levels above 600 ng/ml. In contrast, all patients with metastases at initial presentation had serum levels of more than 500 ng/ml. A weak inverse correlation was observed with tissue expression and serum levels of ICAM-1.

Elevated sICAM levels are not found exclusively in RCC, but have been described in a variety of inflammatory diseases, such as rheumatoid arthritis [19], uveitis [1], acute rejection of renal or liver transplants [32], and common cold in children [25].

In melanoma, expression of ICAM-1 in tumors and detection of sICAM seem to be significantly correlated with a bad prognosis [17, 23]. Thus, sICAM-1 is not a tumor marker with specificity for RCC. Elevated serum levels and low tissue expression of ICAM-1 appear to be correlated with a poor prognosis in RCC. The origin of elevated sICAM-1 is not known at present. It may be secreted by large tumors into the circulation; on the other hand, vascular endothelium may have been activated by immune reactions directed against the tumor, in which case sICAM-1 could be derived from the activated endothelium rather than from the tumor. At present, neither hypothesis is supported by data.

Our data clearly indicate that cell-bound and soluble ICAM-1 may have some correlation with the clinical outcome in patients with RCC.

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