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Alterations in polymeric immunoglobulin receptor expression and secretory component levels in bladder carcinoma

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Summary. To assess the capacity of transitional cells to synthesize and release polymeric immunoglobulin receptor (pIg-R) in bladder carcinoma, we studied the localization of pIg-R in normal and tumor tissues and measured the levels of secretory component (SC) either in the free form or bound to Ig (S-IgA, S-IgM) in the serum and urine of 56 patients with transitional-cell carcinoma (TCC) of the bladder. In the normal bladder mucosa, pIg-R was localized in the cytoplasm and plasma membranes of the superficial cells and on all epithelial cell membranes. In TCC cases, 65% of those studied expressed pIg-R. A marked heterogeneity in pIg-R staining was observed in some tumors. Although a better expression of pIg-R in tumors with a well-preserved epithelial architecture was observed, no correlation was found between pIg-R expression and the grade or stage of the tumors in the patients under study. Three groups were established: (1) in TCC with no complications, serum levels of free SC and S-IgA were significantly increased; (2) in TCC with urinary infections (UI), serum levels of free SC and S-IgA were significantly higher than control values but lay within the same range observed in TCC with no complications and rates of urinary excretion of SC were significantly higher than those in normal subjects; (3) in TCC without UI but with hepatic disorders [high gamma-glutamyl transferase (GGT) activity], there was a correlation between serum S-IgA levels and GGT activity ($r = 0.5$, $P < 0.005$) and serum SC levels were significantly higher than those observed in the other groups. Whereas urinary SC levels appear to reflect urinary infection, serum SC levels, albeit influenced by the hepatic status, may be an additional marker of TCC of the bladder.

Key words: Poly-Ig receptor – Secretory component – Secretory IgA – Bladder carcinoma – Urinary infections

The polymeric immunoglobulin receptor (pIg--R), a member of the Ig superfamily, is synthesized by epithelial cells of mucosae [3]. Part of the molecule is released into biological fluids as soluble secretory component (SC), which is found in a free, soluble form (free SC) and/or bound to pIg as S-IgA or S-IgM [22]. The expression of pIg-R has been reported to be a good marker of epithelial differentiation in colorectal carcinoma [4, 9, 24] and adenocarcinoma of the Fallopian tube [18]. Recently, trace amounts of S-IgA and S-IgM [14] and minute amounts of free SC have been detected in normal human serum [30]. High levels of soluble forms of SC have been reported mainly in the serum of patients with hepatobiliary diseases [32]; they have also been found in the serum of patients with malignant breast and lung neoplasia [8, 25, 27] and hepatocellular carcinoma [11].

The transitional epithelium, which lines a major part of the urinary tract, has unique structural and functional features. The urothelium represents a complex system of cells of different types and stages of differentiation [20]. In cases of malignancies, the most common type of tumor is transitional-cell carcinoma (TCC), which is more often characterized by multifocal lesions and reccurence. Previous studies of pIg-R in the bladder have dealt with tissue localization of the molecule or urinary excretion of S-IgA. Elevated excretion of S-IgA was reported in the urine of patients with lower urinary tract infections [19, 29]. Two controversial studies have been published on patients with TCC. Controversial results have also been obtained from the study of pIg-R localization in normal urothelium [12, 13]. To determine the capacity of transitional cells in normal or TCC tissues to synthesize and release pIg-R, we investigated tissue localization in normal and malignant bladder mucosa and measured levels of SC in urine and serum samples from the same subjects.

Materials and methods

Patients and controls

Serum samples were obtained from 59 patients with TCC of the bladder (50 men and 9 women aged 54–87 years; median, 60 years); 51 of these subjects had undergone a resection of TCC, and samples

of these tumor tissues were taken for study. Epithelium specimens from ten normal bladders were used as controls for immunohistochemical procedures. In all, 7 patients exhibited high levels of gamma-glutamyl transferase (GGT) activity (>85 kIU/l), including 3 with hepatic metastases; 16 subjects showed symptoms of urinary tract infection (bacteriuria, >100,000 ml). In 32 cases, urine specimens were also collected. Serum and urine samples were collected immediately before the tumor ablation and stored at −20°C until use. A total of 41 healthy adults (19 men and 22 women aged 22–92 years; median 40 years) with normal GGT levels served as control subjects for serum SC and S-IgA determinations. Urine specimens obtained from 19 of these subjects were used as controls for measurements of urinary SC and S-IgA levels. Urinary creatinine concentrations were determined using a Chem 1 analyzer (Bayer Diagnostic).

Histological and immunohistochemical procedures

The tissues were routinely processed to prepare paraffin-embedded blocks for histological procedures. Serial sections (thickness, 5 μm) were prepared from each specimen for hematoxylin-eosin staining and immunohistochemistry. The indirect immunofluorescence (IF) method was used for pIg-R detection. The sections were deparaffinized by exchanges in xylene and alcohol. Polyclonal goat anti-human free and bound SC antiserum (kindly provided by Prof. J. P. Vaerman, Institute of Cellular Pathology, Brussels) diluted 1:20 in phosphate-buffered saline (PBS) supplemented with 5% fetal calf serum (PBS-FCS 5%) was applied for 50 min. After three washes in PBS, the sections were incubated for 50 min with fluorescein isothiocyanate (FITC)-conjugated rabbit anti-goat Ig antibodies (Dakopatts) diluted 1:50 (v/v) in PBS-FCS 5%. In control sections, PBS-FCS 5% and normal goat serum were used in place of the primary antibodies. The direct IF method was used for the detection of IgA-containing plasma cells in the same tissues. An FITC-conjugated rabbit anti-human alpha-chain antibody (Dakopatts) diluted 1:50 (v/v) in PBS-FCS 5% was applied for 50 min. The grade of each tumor was determined according to WHO criteria [21]. Two sections of each tumor were examined. A semiquantitative estimate of pIg-R staining was carried out; staining of the normal bladder epithelium was assigned a score of 1 as a reference pattern. When no staining was observed, the tumor was given a score of 0. When the staining was either focal or localized in superficial cells, the samples were scored as 1 and the notation "focal" or "superficial cells" was added.

Immunoassay for SC, S-IgA, and S-IgM measurement

Differential quantification of free SC and S-IgA was performed using an enzyme-linked immunosorbent assay (ELISA) as described in a previous study [30]. As the solid phase, it used monoclonal antibodies that were specific for SC in the free or bound form. The antigen (free SC, S-IgA or SIgM) was revealed by a second peroxidase-conjugated antibody that was specific for the SC alpha or mu chain. Since SC and S-IgA concentrations in urine may primarily depend on urinary outpull, all values were calculated as excretion rates (ER) and were expressed as micrograms of SC or milligrams of S-IgA per gram of creatinine.

DNA flow cytometry

Cells of vesical washes were studied for quantitation of DNA using flow cytometry. Tumors were classified as being nearly diploid or distinctly aneuploid. This procedure has been described and discussed in detail in a previous study [17].

Statistical methods

The nonparametric Mann-Whitney *U*-test was used to assess comparisons between groups. Spearman's rank correlation test was used to evaluate correlations.

Results

Immunohistochemistry for pIg-R and IgA

In ten samples of normal bladder epithelium, staining was observe in the cytoplasm and plasma membranes of all superficial cells and in the basolateral membranes of all epithelial cells using anti-SC antibodies (Fig. 1A). However, in rare cases the immunostaining of pIg-R was heterogeneous in a given section. In 32 of the 51 TCC specimens under study (65%), tumor cells were stained by anti-SC antibodies in the same way (cytoplasm and plasma membrane) as that observed in normal bladder tissue. Several sections showed a marked heterogeneity in pIg-R staining, with some neoplastic cells scoring 0 (Fig. 1B). The expression of pIg-R according to the grade and stage of the tumors is summarized in Table 1.

In noninvasive tumor samples (pTa stage), 21 of 29 cases (72%) were given a score of 1. PIg-R expression in well-differentiated cases (pTaG1) was quite similar to that observed in normal tissues. In the other positive cases, immunostaining with anti-SC antibodies was restricted to cells of the superficial layer (Fig. 1C). Of 22 samples from invasive tumors (pT > 1 stages), 16 (66%) were scored positively (Fig. 1D). In half of the invasive TCC specimens in which tumor cells expressed pIg-R, the epithelial architecture was preserved (pT1 and pT2 stages). In these cases, immunostaining was restricted to superficial cells. Cells undergoing squamous metaplasia were usually negative. In three cases, the three grades of anaplasia were exhibited simultaneously by tumor cells in the same section; in these specimens we observed a loss of pIg-R immunoreactivity from grade 1 to grade 3. However, no statistically significant correlation was found between the pIg-R expression in tumor cells and the grade or stage of the tumor among the 51 tumors under study.

No IgA plasma cells were observed in normal mucosa. In contrast, 22 of the 47 cases (47% of TCC contained IgA plasma cells; 14 of these tumors were also immunostained by anti-SC antibodies. In all, 15 of the tumors without IgA plasma cells expressed pIg-R; the number of plasma cells per section was heterogeneous and was related to the degree of inflammation. There was no relationship between the number of plasma cells and the pIg-R expression in tumors.

DNA ploidy

Of 56 vesical washes, 13 exhibited a unimodal DNA profile, with the DNA index being close to 1, whereas the other 43 vesical washes showed a bimodal profile, displaying 1 peak with a DNA index of 1 and a 2nd peak whose index ranged from 1.2 to 2.2. No correlation was observed

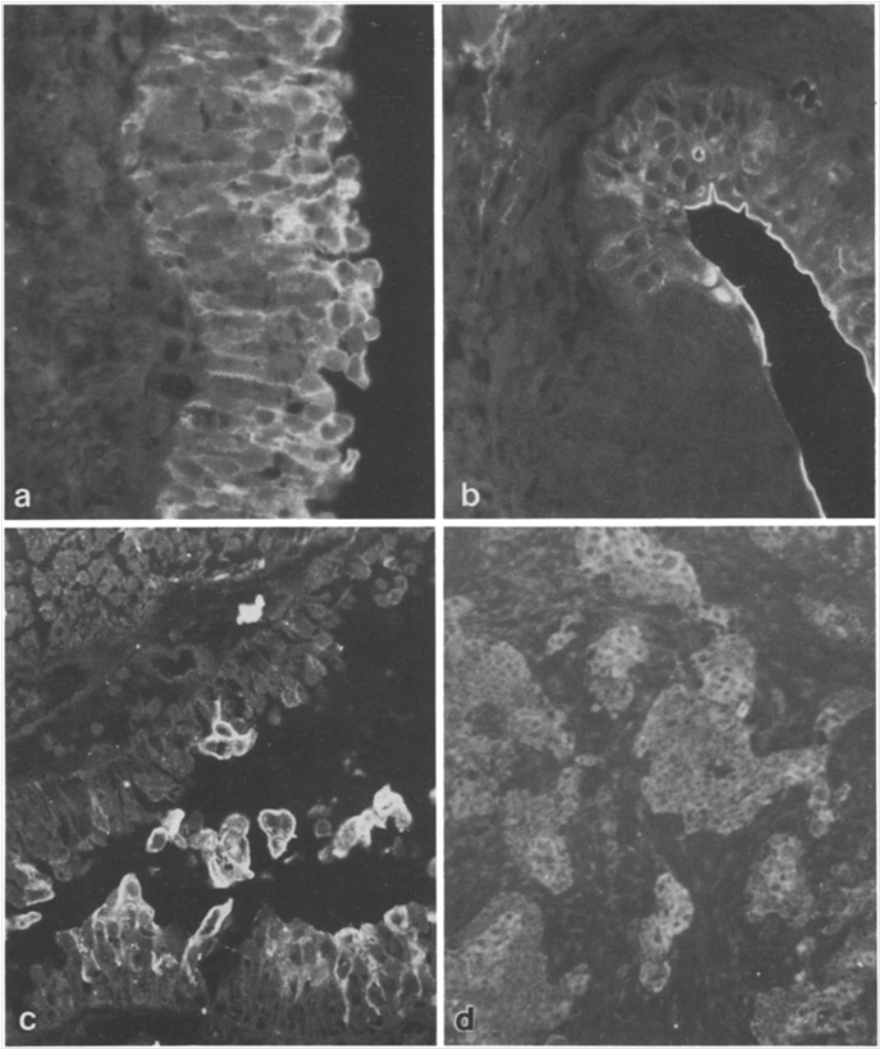

Fig. 1. a Immunofluorescence staining of normal bladder epithelium using anti-SC antibodies: staining of cytoplasm and of the basolateral membrane of superficial cells. ×400. **b** Section of grade I TCC (pTaG1) stained using anti-SC antibodies shows and absence of pIg-R expression by tumor cells. Note the sharp outlines between the normal mucosa and the tumor ×250. **c** Section of grade I (pTaG1) TCC stained using anti-SC antibodies: the staining is localized to superficial cells ×250. **d** Section of invasive grade III TCC (pT2G3): heterogeneous staining of a tumor-cell islet ×250.

Table 1. Expression of the poly-Ig receptor according to the stage and grade of bladder carcionoma

Stage[a]	Tumors (*n*)	Grade[a]	Tumors (*n*)	Poly-IgR expression (*n*)	Focal staining (*n*)	Staining of superficial cells (*n*)
pTa	28	G1	20	14	11	10
		G2	9	6	4	3
		G3	2	1	1	1
pT1	14	G1	1	0	0	0
		G2	4	3	3	2
		G3	9	5	5	2
pT2	7	G2	1	1	1	1
		G3	6	5	4	3
pT3	3	G2	1	0	0	0
		G3	2	2	2	0
pT4	1	G3	1	0	0	0
ISC	3	G3	3	3	3	0

[a] Grade and stage were determined according to WHO criteria [21]. ISC, In situ carcinoma

Table 2. Serum and urinary levels of free and bound SC in patients with TCC of the bladder

	Controls ($n=41$)	TCC patients with high GGT activity ($n=7$)	TCC patients with UI ($n=16$)	TCC patients with no complications ($n=36$)
Serum levels				
CS (μg/l)	0.12 ± 0.05[a] 0.23[b]	0.45 ± 0.32 71% (5/7)	0.23 ± 0.09 43% (7/16)	0.22 ± 0.18 28% (10/36)
S-IgA (mg/l)	3.8 ± 2.3 8.4	20.4 ± 14.3 85% (6/7)	8.2 ± 5.3 37% (6/16)	8.9 ± 8.6 42% (15/36)
S-IgM (mg/l)	6.2 ± 7.9 21.9	6.1 ± 4.8 0 (0/7)	4.4 ± 3.4 0 (0/16)	4.6 ± 3.1 0 (0/36)
urinary levels	($n=20$)	($n=2$)	($n=8$)	($n=24$)
SC (μg/g creatinine)	61 ± 65 191	510 ± 183 100% (2/2)	263 ± 194 50% (4/8)	175 ± 295 12.5% (3/24)
S-IgA (mg/g creatinine)	0.47 ± 0.37 1.22	6.57 ± 3.98 100% (2/2)	2.65 ± 2.80 62% (5/8)	1.81 ± 3.47 17% (4/24)

[a] Mean ± SD
[b] Mean ± 2 SD
[c] Percentage (number of patients) above the mean + 2 SD
UI, Urinary infection

between the cellular DNA content and either the grade or stage of TCC or the pIg-R expression in washes.

Serum and urinary levels of free and bound SC

Normal subjects. In control subjects, serum levels of free SC, S-IgA, and S-IgM averaged 0.122 ± 0.052, 3.81 ± 2.28, and 6.2 ± 7.9 mg/l, respectively (Table 2). No S-IgM was detected in the urine of healthy subjects or TCC patients. In control subjects, the ER for free SC averaged 61 μg/mg creatinine and that of S-IgA averaged 470 μg/g creatinine; the upper limit of normal values was 226 μg/g creatinine for SC and 1.22 mg/g creatinine for S-IgA. We studied separately the following three groups of TCC patients: Those displaying no complications, those presenting with urinary infections (UI), and those exhibiting high serum GGT activity.

TCC patients showing no complications. Serum levels of S-IgA and free SC (8.9 ± 8.6 and 0.22 ± 0.18 mg/l, respectively) were significantly higher in these patients than in normal subjects. The urinary ERs for S-IgA and SC were in the same range as those of control subjects. S-IgM levels (5.61 ± 3.68 mg/l) were similar to those of controls. A positive correlation was shown between serum levels of free SC and those of S-IgA ($r=0.5$, $P<0.005$). No correlation was found between pIg-R expression by tumor cells and serum levels of SC or S-IgA. No relationship could be found between serum SC levels and the urinary ER for SC or between the number of IgA-containing plasma cells and the urinary ER for S-IgA.

TCC patients with urinary infections. S-IgA and free SC serum levels (8.2 and 0.232 mg/l, respectively) were significantly higher in these patients than in the control group but lay within the same range observed in TCC patients who exhibited no complications. The urinary ER for S-IgA and SC were significantly elevated as compared with those measured in control subjects and in TCC patients showing no complications ($P<0.001$).

TCC patients exhibiting elevated GGT activity. Serum levels of S-IgA and SC (20.4 and 0.451 mg/l; $P<0.001$ and $P<0.005$, respectively) in these patients were significantly higher than those measured in control subjects or in TCC patients displaying no elevation in GGT activity. Interestingly, a correlation was found between S-IgA values and GGT levels ($r=0.5$, $P<0.005$). S-IgA levels did not seem to be influenced by the presence or absence of hepatic metastasis. In one case, normal GGT activity and normal S-IgA and SC levels were observed despite the presence of liver metastasis; in four cases, elevated levels of both GGT activity and serum SC were observed in the absence of liver metastasis. Urine samples were studied in only two patients from this group; the ERs for S-IgA and SC were above normal values in both cases. No relationship was found between DNA ploidy and serum or urinary SC levels, regardless of patient group studied.

Discussion

The present study showed that significantly elevated serum levels of S-IgA and free SC occurred in patients with bladder TCC. The correlation between serum levels of S-IgA and GGT activity in the group of TCC patients exhibiting high serum GGT activity has previously been reported in individuals presenting with various hepatic disorders [32]. Elevated S-IgA levels have been shown to

be a good indicator for hepatic metastases in large-bowel and breast carcinomas [15, 16], and the present study extended this finding to patients with TCC and liver metastases. However, this is the first report of high levels of SC in the serum of TCC patients exhibiting normal GGT activity in the absence of urinary infections. These high levels may have been due to the dissease itself, since elevated S-IgA levels have been reported in other epithelial cancers [8, 25]. Further study of the mechanisms of transport of SC from the tumor to the serum is necessary, as no relationship could be found in the present study between serum levels of SC and the stage or grade of TCC or between SC levels and pIg-R expression in TCC patients.

In normal subjects, both serum levels and the urinary ERs for free SC and S-IgA were in agreement with previous findings [10, 19, 30]. The absence of the S-IgA/IgA correlation reported by Marx et al. [19] in the urine of patients suggests a local synthesis of S-IgA and SC in the urinary tract mucosa. Elevated ERs for S-IgA have previously been reported in urinary infections [19]. In the present study, the ERs for SC were higher in TCC patients exhibiting urinary infection than in controls or in the other TCC patients. Such an elevation could reflect the secretory activity of the entire urothelium rather than a local immune reaction in the bladder, since the quantity of IgA plasma cells detected in the bladder mucosa of subjects with urinary infections was no higher than that found in the bladder of TCC patients who did not have infection. Our results are supported by similar observations made by Trinchieri et al. [29] in urinary infections. Indeed, ultrastructural studies have shown that bacteria can be eliminated via mechanical processes involving mucous secretions without the direct involvement of specific immune reactions [1]. SC molecules secreted at the apical pole of the superficial cells could play a role in this nonspecific mechanism.

In normal bladder mucosa, pIg-R was detected on basolateral membranes of basal and intermediate cells, in the cytoplasm, and in membranes of superficial cells. Previous studies have described different patterns of pIg-R expression, which occurs either exclusively within superficial cells [28] or in a thin layer at the surface of such cells in association with small amounts in the cytoplasm of intermediate cells [12]. Another study had described the expression of SC bound to IgA in all layers of the urothelium [13]. These discrepancies might be due to the immunoreactivity of the antiserum used. Our goat antiserum, which is specific for the soluble forms of pIg-R (free and bound SC), can be used in routinely paraffin-embedded material without the need for protease treatment. Its specificity has been documented in previous studies [6]. Localization of pIg-R in the present study was the same as that described for cytokeratin by Moll et al. [20]. As suggested by the pattern of expression of cytokeratin [7, 20], the pIg-R pattern expression confirms that differentiation of cells in the transitional epithelium can be inverted in relation to that in other epithelia [7, 20].

In tumor tissues, we observed that pIg-R localization was modified (lost or reduced) in 55% of cases. An interesting and unexpected result was the heterogeneity of pIg-R localization. Our study did not confirm the decrease in pIg-R expression with increasing tumor grade previously described by Kirkham et al. [12]. In most instances, expression of pIg-R varied within a given tumor sample, suggesting that independent mechanisms regulate such expression. This heterogeneity in pIg-R expression was similar to that observed in other tumor-associated antigens of TCC [2, 20]. Clonal analysis of TCC of the bladder has demonstrated tumor heterogeneity in a given tumor biopsy [5]. The lack of correlation between pIg-R expression and cellular DNA content might have been due to a low number of cells or to the aforementioned tumor heterogeneity of pIg-R expression. Expression of pIg-R could be considered an additional marker that can be used to phenotype bladder tumor cells in association with other epithelial antigen markers (cytokeratin, epithelial membrane antigen, carcinoembryonic antigen) [20, 23, 33] or with oncogene products such as p21 protein [31]. Another interesting finding was the localization of pIg-R in the superficial cells of positive cases in which the epithelial architecture was preserved, regardless of the degree of differentiation of tumor cells or the stage of invasion of the tumor.

A recent study has shown that the loss of particular genic activities can be responsible for the high metastatic potential of tumor cells [26]. The heterogeneity in the expression of pIg-R may be related to the difference in tumor behavior associated with more or less invasive and metastatic potential. For instance, the preservation of pIg-R expression by superficial cells at the time of diagnosis could signify a relatively good prognosis for a given tumor. This hypothesis is currently being tested in a clinical follow-up of TCC patients.

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