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Carcinoembryonic Antigen in Serum, Urine and Cells of Patients with Bladder Carcinoma

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Summary. A raised level of CEA-like substance has been demonstrated by radioimmunoassay in the urine of patients with bladder carcinoma, in concentrations which increase with a more advanced stage, and in serum of patients with advanced disease. In a 2-year follow-up of patients receiving chemotherapy, a correlation of raised urinary CEA to local recurrence was seen, as well as rising and high serum values with metastases. In the patients who responded to treatment, CEA values became normal. CEA was also located in carcinoma cells from bladder washings in 24-61% of the cases. Combined studies of CEA in serum, urine and cells may be used to study the biology of the tumour and perhaps also in the monitoring of patients with urothelial carcinoma.

Key words: Bladder Cancer.

Carcinoembryonic antigen (CEA), one of the fetal substances occurring in high amounts in colonic and rectal adenocarcinomas (3), has now been found with other tumours. In urine from patients with urothelial carcinomas, Nery et al. (7) found urinary UCEA-1 of a molecular weight similar to that of CEA. UCEA-2 was related in molecular size to a non-specific cross-reactive antigen (NCA) and UCEA-3 was characterised by its larger molecular weight, possibly the same as the large-sized urinary molecules with CEA reactivity described by Wu et al. (12). We and others, have demonstrated UCEA-1 in urine not only of bladder carcinoma patients but also of healthy persons and in inflammatory changes of the bladder (1, 4, 5, 6, 8, 10, 11). A CEA-like substance, BCEA-1, was extracted from two primary carcinomas of the bladder (13). The main part of this CEA-like substance was immunologically similar to CEA from colonic carcinoma and is now being further characterised (14).

In this paper clinical situations are described in which CEA determinations may be helpful.

MATERIALS AND METHODS

Patients

Patients with bladder tumours were seen at the Department of Urology and at Radiumhemmet, Karolinska Hospital. Tumours were diagnosed by intravenous pyelography, cystoscopy with bimanual palpation under anaesthesia, biopsy and cytological smears from bladder washings. The clinical stage and histopathological grade of malignancy were always determined. The treatment consisted of surgery and/or radiation treatment for primary tumours (2) and mostly intravenous chemotherapy for recurrences. Urine was collected repeatedly for sediment analysis, bacterial culture and CEA determination.

Radioimmunoassay (RIA)

Serum and urine determinations of CEA were performed on perchloric acid (PCA) extracted samples according to instructions with the Hoffmann-La Roche kit (Basle). A double-antibody RIA (9) was used alternatively.

Immunofluorescence (IF)

Bladder washings were obtained at the same time as the cystoscopic examination. Smears were made for cytological evaluation and for immunofluorescence. Indirect immunofluorescence was performed with specific rabbit anti-CEA and sheep anti-rabbit IgG. Cell populations

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Table 1. CEA in urine of patients with primary bladder carcinoma

Clinical stage	No. of patients	CEA in urine, ng/ml	% positive (⩾30 ng/ml)
T1	2	18	0
T2	27	40[a]	59
T3	26	43[b]	61
T4	15	68[c]	67
	70		
Healthy persons	13	18	0

Difference compared to healthy persons (Student's t-test) [a] $p<0.1$, [b] $p<0.01$, [c] $p<0.001$

Table 2. CEA in serum of patients with primary and recurrent bladder carcinoma

Clinical stage	No. of patients	CEA in serum, ng/ml
T1	2	1.5 ± 2
T2	16	3.9 ± 2.7
T3	14	5.6 ± 4.6[c]
T4	15	5.4 ± 3.8[c]
Recurrent tumour	48	5.8 ± 8.0[b]
Metastases	12	8.0 ± 7.1[c]
Tumour free after irradiation	56	2.3 ± 1.9
Healthy persons		<3

Degree of significance, see Table 1

with more than 5% CEA IF positive tumour cells were considered positive (9). No reactions with non-specific cross-reacting antigen were seen.

RESULTS

Patients with untreated bladder carcinoma had higher urinary CEA values in more advanced clinical stages (Table 1). CEA values varied greatly between individuals. Even so, 34 patients who recovered after radiation therapy all developed normal urinary CEA values, while urinary CEA remained high in 70% of the patients where the tumour persisted. Bacterial infections in addition to tumour gave high CEA levels in a few cases where resistant bacteria were encountered, but mostly no infections were seen. Serum values were significantly increased in patients with T3 and T4 tumours, recurrence and metastases (Table 2). Determination of carcinoembryonic antigen in urine and serum may therefore be of clinical assistance in evaluating regression or progression of urothelial carcinomas.

Table 3 presents CEA values of patients with recurrent bladder carcinoma or metastases before the start of chemotherapy. The frequency of raised urinary CEA levels is higher (91%) with a local recurrence than with metastasis, although 11 of the 20 patients with metastasis also had local recurrence.

Rising urinary CEA values were seen with progression of the local tumour in 18 cases. Low or decreasing values were seen with regression in two cases. One patient with no macroscopic tumour but a cytological recurrence had a low CEA urinary value, as did two patients with a macroscopically visible recurrence. The remaining patients had static disease during the study.

In metastatic disease, the serum CEA values were increased above 2.5 ng/ml in 14 out of 20 patients. With regression following chemotherapy, a decreased serum CEA was seen in the two patients who responded well to therapy. Of 17 further patients with treated bladder carcinoma and no evidence of recurrence or metastasis, 13 had low serum CEA values, while 4 repeatedly had raised serum CEA's without clinical evidence of metastases. In the latter group it would be particularly important to follow-up closely to detect possible metastases.

CEA was also demonstrated by immunofluorescence in the carcinoma cells of bladder washings (9). Among the more highly differentiated cell populations, 14 out of 23 such patients (61%) had CEA IF positive cells in their smears. In low differentiated or anaplastic cell populations, CEA-containing cells were seen in only 4 out of 17 patients (24%). The urinary CEA of these patients was above 20 ng/ml in all the 22 cases in whom it was measured. Normal urothelial cells from 22 patients did not stain for CEA.

DISCUSSION

Our aim was to study the relationship between urinary, serum and urothelial cancer cell CEA

Table 3. CEA in urine and serum of patients with bladder carcinoma before chemotherapy

Clinical stage	No. of patients	mean CEA, ng/ml			
		in urine	% positive patients (>30 ng/ml)	in serum	% positive patients (>2.5 ng/ml)
Recurrent tumour	33	54	91	4.1	64
Distant metastases (also local recurrence in 11 patients)	20	56	65	5.9	70

contents. Indirect evidence pointed to a release of CEA from bladder carcinoma: During irradiation of bladder cancer the urinary CEA is highest in mid-course when the tumour breaks down and diminishes towards the end of treatment (10); Urinary content of CEA is related to the clinical stage, size, mode of invasion, and cytology (6, 10) but not to the plasma CEA levels (8, 12). This points to CEA or a CEA-like substance being actively synthesised within the urinary system.

The urines contain RIA inhibitory material, which was removed by PCA extractions, thereby departing from the definition of CEA. This material contributed 30-90% of the original CEA-like reactivity in urines of bladder carcinoma patients (13). The exact nature of the RIA inhibitory material is not known. In addition to CEA, perhaps antibody to CEA may be formed locally. Also mucinous material may be inhibitory in the RIA. For the practical use of urinary CEA determinations, it is thus essential to perform PCA extraction and use critically NCA-absorbed antisera. Under such conditions, CEA determinations of urines and sera have proved valuable in the follow-up bladder cancers.

It appears that tumour progression to a more malignant state involves the loss, or decreased synthesis, of CEA. CEA-containing cells can be demonstrated in 60% of well to moderately well differentiated urothelial carcinomas. A comparison of RIA results with IF detectable above background implies the possibility of detecting less than 1 pg CEA/cell in unfixed carcinoma cell specimens (9). Quantitative CEA determinations in cells of bladder washings will continuously be performed to study the prognostic value of this procedure.

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