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Experiences with SCC Antigen, a New Tumor Marker for Cervical Carcinoma

W. MEIER,* W. EIERMANN,* P. STIEBER,† A. SCHNEIDER,* A. FATEH-MOGHADAM† and H. HEPP*

*Department of *Obstetrics and Gynecology and †Clinical Chemistry, Klinikum Grosshadern, Ludwig-Maximilians-University Munich, Marchioninistr. 15, 8000 München 70, F.R.G.*

Abstract—*Squamous cell carcinoma (SCC) antigen was first described by Kato* et al. *in patients with carcinoma of the cervix uteri. SCC serum levels can be measured with a radioimmunoassay. In our investigation,* 2.0 ng/ml *was taken as the upper limit of the standard range.*

In 35 *healthy women there were no elevated SCC serum levels. Eight of* 40 *patients with breast, endometrial and ovarian cancer had raised SCC levels. In only two of* 12 *patients with benign gynecological diseases, SCC was also elevated. Sixty per cent of the patients with primary and* 73% *of the patients with recurrent cervical cancer showed pathological values; CEA was elevated in* 31% *and* 51% *respectively. The absolute values increased with the stage of the disease. Sixty-nine per cent of patients with squamous cell carcinoma had elevated levels. In five of nine adenosquamous carcinomas SCC was pathological.*

SCC shows a high sensitivity for squamous cell carcinomas of the cervix uteri. The tumor marker might be helpful in the control of primary therapy and follow-up of cervical cancer patients.

INTRODUCTION

ALONGSIDE clinical, biochemical and radiological investigation, tumor markers are becoming increasingly important in oncology. For some tumors, e.g. chorioncarcinoma and ovarian carcinoma, there are tumor markers already available for routine use [1–3].

There have been several recent reports on CEA and TPA in gynecological malignancy. However, these markers remain without practical relevance [4–7]. Up until now there has been no reliable parameter available in cases of cervical carcinoma for controlling the success of primary therapy and follow-up. Kato *et al.* first described a tumor antigen (TA-4) in patients with cervical carcinoma [8–11]. SCC (squamous cell carcinoma) antigen is a fraction of TA-4 and can be found in high concentrations in the tissue of cervical carcinoma. It is also found at a lower concentration in normal squamous cell epithelium [9]. The development of a radioimmunoassay has made the estimation of SCC in serum possible and thus the use of SCC as a tumor marker.

This study was undertaken to investigate the clinical importance of SCC antigen for diagnosis, primary therapy and follow-up in patients with cervical cancer. Furthermore, SCC antigen was compared with the tumor marker CEA, which has been used most frequently to date.

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PATIENTS AND METHODS

From January 1985 until April 1987, 135 patients with primary cervical carcinoma were treated in the Department of Obstetrics and Gynecology, of Grosshadern Hospital, University of Munich. SCC antigen levels were determined in 35 healthy women, 12 patients with benign gynecological disease, e.g. uterine fibroids, endometriosis and benign ovarian tumors, 40 women with primary breast, endometrial and ovarian carcinoma and 154 patients with cervical carcinoma. Included in the latter group were 80 of the 135 women with primary carcinoma, 37 patients with recurrent disease and 37 patients in remission. Blood samples were obtained pre- and postoperatively and every 1–3 months during follow-up. Follow-up investigations were performed every 3 months with blood sampling and gynecological examination. Computed tomography was performed once a year regularly during the first 3 years or in those cases with suspected recurrence.

Tumor staging was performed using the FIGO classification. Treatment was dependent on the clinical stage of the disease. In stage I and II disease, a radical hysterectomy with paraaortal and pelvic lymphonodectomy was performed whenever possible. In stage III and IVa, primary radiotherapy was carried out, which consisted of external irradiation of the pelvis (4000–4500 rad) and intravaginal radium applications (2500–3000 rad).

Three patients with stage IVb disease were treated primarily with cytostatic drugs.

Serum levels of SCC antigen were determined using a radioimmunoassay (Abbott); 2.0 ng/ml was taken as the upper limit of normal. CEA levels were determined using an enzyme immunoassay from Abbott. The upper limit of normal was taken as 3.0 ng/ml.

Statistical significances were calculated by the Mann–Whitney test. The differences were considered statistically significant when the P value was <0.05.

RESULTS

None of the 35 healthy women had raised SCC levels. Two of 12 patients with benign gynecological disease had raised SCC levels of more than 2.0 ng/ml (see Table 1). There was one patient with a benign serous cystadenoma of the left ovary and one patient with uterine fibroids. Eight of 40 patients with breast, endometrial and ovarian carcinoma had raised SCC levels. Of the four patients with ovarian cancer, there were two women with serous cystadenocarcinomas, one with an endometrioid carcinoma and one with an undifferentiated tumor. There were no cases of squamous cell carcinoma of the ovary. Sixty-four per cent of the women with primary cervical carcinoma or recurrent disease following successful primary therapy demonstrated pathological SCC levels. In contrast, the CEA values were only raised in 38% of these patients. One patient in the group of women in remission showed a SCC level of more than 2.0 ng/ml on one occasion. This patient has been followed now for 17 months and there is no evidence of recurrent disease. Five of the patients in the remission group had false positive CEA levels.

In Table 2, the results are shown arranged according to stage of disease. Three of nine women with stage Ia had raised SCC levels; CEA was normal in all these patients. In stage Ib, 11 of 23 patients had raised SCC levels compared with three with raised CEA levels. In stage II, 12 of 20, in stage III 14 of 16 and in stage IV eight of 12 patients had pathological SCC levels. In stage II, III and IV the CEA levels were raised in seven, seven and eight patients respectively. Altogether, 60% of patients demonstrated raised SCC levels before treatment. In comparison, CEA levels were only raised in 31%. There were no statistically significant differences in SCC levels between the stages. The confidence interval for stage Ia was 0.78–2.31, for stage Ib 1.53–4.84, for stage II 1.54–15.57, for stage III 2.68–16.96 and for stage IV 18.31–126.49. The mean SCC value rose with advancing disease from 3.2 ng/ml in stage Ib to 54.0 ng/ml in stage IV disease.

In radically operated patients without remaining tumor, the SCC antigen levels fell rapidly following therapy (Fig. 1). If a complete resection was not possible, SCC levels remained raised. Twenty-six of 33 patients with primary radiation therapy showed elevated SCC levels initially. In contrast to the rapid decrease in patients with radical hysterectomy the SCC values decreased gradually and dropped to less than 2.0 ng/ml at the end of radiotherapy. Figure 2 gives one example out of 26 patients with initially elevated SCC levels and radiotherapy.

Twenty-seven of the 37 patients with recurrent disease after successful primary therapy demonstrated SCC levels of more than 2.0 ng/ml. CEA was raised in 19 cases (Table 3). Twenty-five patients had a local recurrence, including recurrence at the vaginal stump and tumor on the pelvic walls. SCC was raised in 19 cases, CEA in 10 cases. In patients with distant metastases (lung, bone and supraclavicular lymph nodes), eight women had raised SCC levels and nine raised CEA levels. There was no statistical difference between local recurrence and distant metastases. The increase in SCC antigen preceded the clinical or radiological detection of recurrence in 22 patients by 1–7 months with a median lead time of 3.3 months (standard deviation: 1.5 months). SCC levels appear to be higher in patients with a recurrence compared with patients with primary disease. Figure 3 shows the course of disease and the SCC values in one patient, who developed a suburethral recurrence 2 years after radical hysterectomy. The increase in the previously normal SCC levels occured 4 months before the clinical diagnosis of recurrent disease. Following excision and radiotherapy, the SCC levels

Table 1. Frequency of elevated SCC serum levels in healthy women and patients with different gynecological tumors

	n	SCC > 2 ng/ml	
Healthy women	35	0	(0%)
Benign gynecological disease	12	2	(17%)
Breast carcinoma	10	1	(10%)
Endometrial carcinoma	10	3	(30%)
Ovarian carcinoma	20	4	(20%)
Cervical carcinoma	117	75	(64%)

Table 2. SCC and CEA serum levels in patients with cervical carcinoma

FIGO	*n*	SCC > 2 ng/ml *n*	Mean value ng/ml(range)	CEA > 3 ng/ml *n*
IA	9	3	1.5 (0.6–3.2)	—
IB	23	11	3.2 (0.2–16.9)	3
II	20	12	8.6 (0.2–63.8)	7
III	16	14	9.8 (1.2–56.9)	7
IV	12	8	54.0 (0.2–396.0)	8

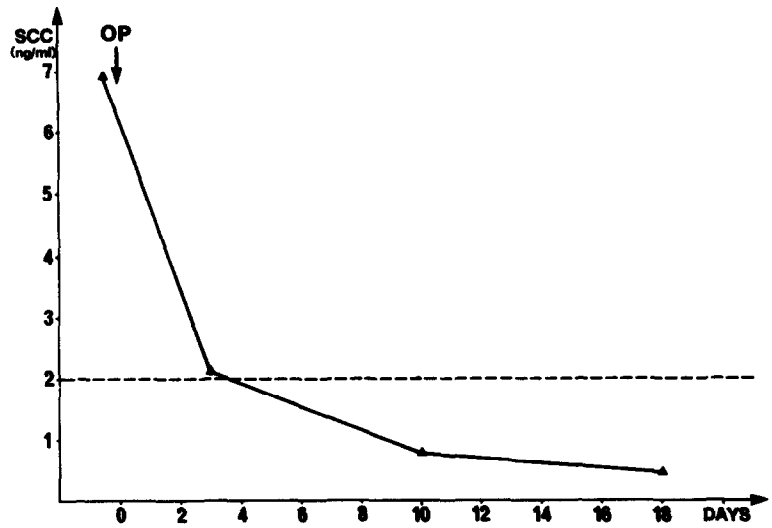

Fig. 1. SCC levels after radical hysterectomy in a patient with cervical carcinoma stage IB.

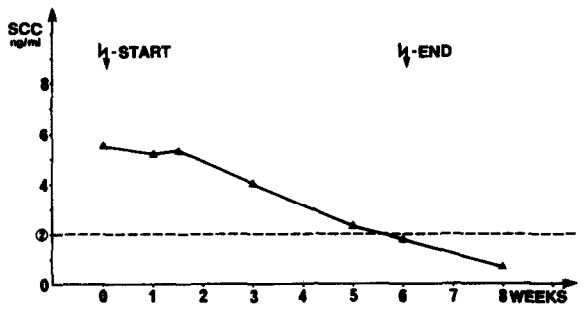

Fig. 2. SCC levels during radiotherapy in a patient with cervical carcinoma stage IIIB.

decreased but remained pathological. A second rise corresponded with the discovery of pulmonary metastases. The patient is now receiving chemotherapy.

The incidence of elevated serum SCC levels in cervical carcinoma is related to the histological appearance (Table 4). In squamous cell carcinoma 68 of 99 patients (69%) demonstrated raised levels. The CEA levels were pathological in only 31 patients (31%).

In patients with adenosquamous carcinoma, the SCC antigen was raised in five of nine, CEA in six of nine cases. In nine cases of adenocarcinoma, only three had raised SCC levels. CEA levels were also pathological in three cases.

When both markers were estimated together, 90% of patients with recurrent squamous cell carcinoma had elevated levels. In these cases SCC was elevated in 83%, CEA in 48%. In cases with adenosquamous carcinoma, simultaneous tumor marker estimation led to raised levels of either SCC, CEA or both in eight of nine cases; SCC was pathological in five, CEA in six cases. In patients with adenocarcinoma and estimation of both markers, six of nine patients had raised levels.

Table 3. SCC and CEA serum levels in patients with recurrent cervical carcinoma

	n	SCC > 2 ng/ml	CEA > 3 ng/ml
Local recurrence	25	19	10
Distant metastasis	12	8	9
Total	37	27	19

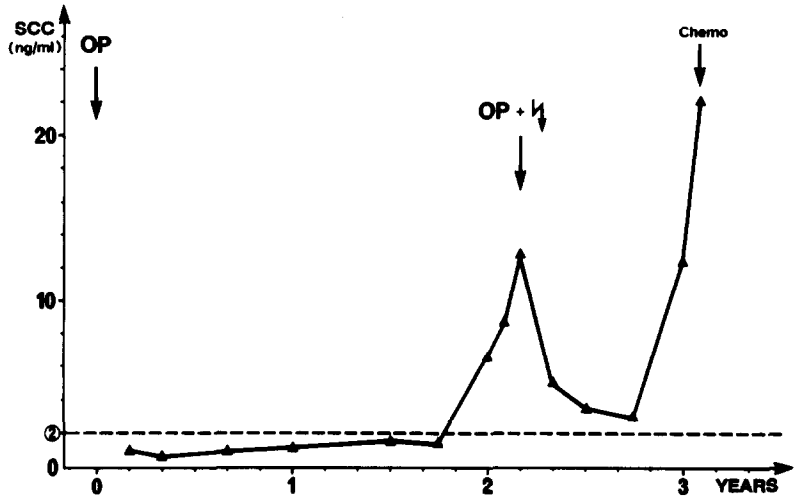

Fig. 3. SCC levels in a patient with suburethral recurrence and pulmonary metastases.

Table 4. SCC and CEA serum levels depending on histology

	n	SCC > 2 ng/ml	CEA >3 ng/ml	Elevated SCC and/or CEA serum levels
Squamous cell carcinoma	99	68	31	70
primary therapy	70	44	17	46
recurrence	29	24	14	26
Adenosquamous carcinoma	9	5	6	8
Adenocarcinoma	9	3	3	6

DISCUSSION

Our results confirm the observations from other groups, that SCC is a sensitive tumor marker for cervical carcinoma [10, 12–15]. If 2.0 ng/ml is taken as the upper limit of normal, 60% of women with primary cervical carcinoma have raised SCC serum levels. In contrast, the sensitivity of CEA is clearly lower with only 31% having raised values. In cases of recurrent disease, the figures are similar. SCC is raised in 73%, CEA in 51% of cases. There is a clear correlation with the histological tumor type. Sixty-nine per cent of patients with squamous cell carcinoma demonstrated pathological SCC levels. Over 50% of cases with adenosquamous carcinoma had raised SCC levels. Other tumor markers such as TPA and CEA show an obviously lower sensitivity in cases of squamous cell carcinoma [4, 5, 7]. SCC serum levels were also raised in other gynecological malignancies, e.g. ovarian, endometrial, breast carcinoma [14].

From these results, we can conclude that SCC is an ideal tumor marker for monitoring the primary therapy and treatment of recurrent disease and that it can be used for follow-up control [10, 11, 13, 14]. SCC is, however, of little or no value as a screening method, especially when the high success rate of cytological screening is considered.

SCC levels in the follow-up correlated well with the clinical course of the disease [9, 12, 13]. Only one of 37 patients in remission demonstrated an elevated SCC level over 2.0 ng/ml following successful primary treatment. On the other hand, five of 37 patients in remission had raised CEA levels (false positive). In none of these cases of false positive CEA levels could a gastrointestinal disease be found. Seventy-three per cent of patients with recurrent disease had raised SCC levels. In some cases, the pathological levels preceded the clinical diagnosis by several months. An increase in SCC antigen should raise the suspicion of recurrence and patients should be controlled carefully and regularly.

The level of SCC antigen is obviously related to the stage of disease [10, 12, 14, 15]. While 44% of patients with stage I disease had raised SCC levels, in stage II 60% demonstrated elevated levels. The absolute value also increases with disease progression, from 3.2 ng/ml in stage Ib to 54.0 ng/ml in stage IV disease. Similarly, a correlation with disease staging can also be demonstrated for CEA. In stage I only three of 32 patients had raised CEA levels, in stage III and IV over 60% of patients had elevated levels.

If both markers are estimated, 70% of cases with squamous cell carcinoma show raised levels; in

cases with recurrent disease this increases to 90%. Adenosquamous carcinoma leads to an incidence of 55% raised SCC levels alone or 89% raised combined levels. For follow-up of cases with squamous cell carcinoma, SCC alone is satisfactory; for cases with adenosquamous carcinomas and adenocarcinomas the combination of both markers is better.

As a result of data already published [8–10, 12, 14, 15] and our results, one can conclude that SCC antigen is superior to the most commonly used marker CEA in cases of cervical carcinoma. The use of SCC antigen as a marker to monitor the success of therapy and in follow-up squamous cell carcinoma of the uterine cervix appears to be justified. Further investigation is needed to show whether our preliminary results can be confirmed on a larger population.

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