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Serum CEA Monitoring in the Follow-up of Colorectal Cancer Patients with Negative Preoperative Serum CEA

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Abstract—*Thirty-nine patients with colorectal cancer and normal preoperative levels of carcino-embryonic antigen (CEA) were followed up with serial CEA determinations and with complete clinical and laboratory work-ups for the detection of tumor recurrence, for at least* 1 yr *after surgery. The same schedule for serum CEA assay and other clinical and laboratory tests was followed, for comparison, in* 32 *colorectal cancer patients with elevated preoperative serum CEA titers, and in whom surgery had been followed by a return to normal of the CEA values. In the follow-up group with negative preoperative serum CEA values,* 66.7% *of the patients had normal serum CEA titers, and* 60% *were free from symptoms of tumor recurrence after* 1 yr *from surgery. Whereas,* 28.2% *of the patients of this group showed a steady rise of their serum CEA levels after periods ranging from* 3–12 months *from surgery; this serum CEA elevation preceded in nine of these patients other evidence of tumor recurrence by* 3–5 months *in the average. The above pattern was superimposable to that observed in the patients with positive preoperative serum CEA, about one third of whom exhibited a steady rise of serum CEA to abnormal values (as an early indicator of tumor recurrence) in the first year after surgery.*

The present results point out the relevant value of monitoring the serum CEA titers also in the postoperative follow-up of patients with normal preoperative serum CEA, since about one third of these patients may develop steadily rising serum CEA levels as an early indicator of tumor recurrence in the first year after surgical treatment.

INTRODUCTION

Almost 15 yr since its first description [1, 2], the carcino-embryonic antigen (CEA) is now-a-days the object of a renewed wave of interest. In fact, the introduction into use of more and more feasible methods for the routine assay of serum CEA has resulted in the accumulation of a great deal of data clarifying its behavior in the course of treatment of various malignancies [3]. As a matter of fact, the value of routinary serum CEA assays has been well established for monitoring the tumor response to therapy [4–6], when high CEA titers fall to normal values following total resection of the tumor lesions [7], or during chemotherapy [8–10] or radiotherapy of the tumor lesions [10, 11]. This use of serial CEA assays is particularly important for the early detection of tumor recurrence in patients submitted to resection of a colorectal cancer; in fact, due to the tendency of this tumor to show both distant metastases and local recurrences, these patients may derive some benefit from a 'second-look' surgery, decided on the basis of raised serum CEA levels as an early indicator of tumor recurrence [12–14].

In this regard, colorectal cancer patients to be followed up postoperatively with serum CEA monitoring are usually selected on the basis of a raised preoperative serum CEA value [6, 7, 15–18]. Whereas, little is reported in the literature about the postoperative se-

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rum CEA follow-up of patients with negative preoperative values [13, 15, 19–21]. We intend to report here briefly on the preliminary results obtained in a series of colorectal cancer patients with normal preoperative CEA values, in whom the serum CEA levels have been monitored in the first year following resection of the tumor. The results of such follow-up have been compared with those obtained in a group of patients with positive preoperative serum CEA levels.

MATERIALS AND METHODS

Patients

A total of 39 patients (23 men and 16 women, mean age 60.2 ± 11.6 yr) submitted to resection of a colorectal cancer were selected for this study, on the basis of normal preoperative serum CEA values. Histology revealed adenocarcinoma in all cases. Heavy smokers (more than 15 cigarettes/day) and patients with known, or suspected alcoholic hepatitis were excluded from the present study. Concerning the stage of the tumors, five of these patients (12.8%) had a Dukes A colorectal cancer, 18 a Dukes B (46.2%), 14 a Dukes C (35.9%), and two (5.1%) had a Dukes D tumor.

All patients had a blood sample taken for CEA assay preoperatively, then at the 4th and 14th day after surgery. Subsequent blood samples were taken at regular intervals (every 2–3 months) in the following 12–20 months, on the occasion of follow-up examinations; the complete work-up of the patients included physical examination, chest standard X-ray, recto-sigmoidoscopy, liver scan, hemogram and liver function tests; barium enema and bone scan were performed when indicated.

Aliquots of serum for the CEA assays were separated after centrifugation within 2 hr after drawing, and stored at −20°C until assayed. Before the assay, the thawed samples were centrifuged at 3000 rev/min for 5 min.

A similar schedule for the postoperative follow-up was applied also to 32 patients (18 men and 14 women, mean age 62.1 ± 13.2 yr) with colorectal cancer and raised preoperative serum CEA, in whom surgery had been followed by a return to normal of the CEA titers; this group served to define the control pattern of serum CEA elevations as an early warning of tumor recurrence, according to the common protocols reported in the literature. Staging of the tumor showed that two of these patients (6.2%) had a Dukes A colorectal cancer, 10 a Dukes B (31.2%), 14 a Dukes C (43.8%), and six (18.8%) had a Dukes D tumor.

CEA assay

CEA levels were directly measured in serum by radioimmunoassay (RIA), using commercial CEAK kits (purchased through SORIN Biomedica, Saluggia, Italy) based on a double antibody method [22]. The levels measurable in the serum of healthy individuals by this method result to be somewhat higher than with the original RIA method, implying the perchloric acid extraction of CEA from serum [23, 24]. Thus, the upper limit of normal for non-smokers is 10 ng/ml with this direct technique, as compared to 2.5 ng/ml with the previous methods [23, 24]. This is possibly due to the presence of interfering background substances in unextracted serum [5]: anyway, the response of this assay parallels the response of the previous methods, both in normals and in patients with elevated serum CEA concentration [5].

The significance of the serum CEA elevations in the individual patients was evaluated on the basis of the intra-assay and interassay variabilities of the RIA system observed in our laboratory, by developing a CEA nomogram according to the procedure described by Martin and coworkers [12]. Moreover, an increased CEA value was always confirmed by repeated assays of the same sample, and by assaying an additional sample obtained from the same patient.

RESULTS

In 18 out of the 39 patients with normal preoperative serum CEA (46.2% of this group) a transitory rise of the serum CEA levels (never higher than 20 ng/ml) in the first postoperative week occurred, and was followed by a return to normal by the 4th postoperative week.

After an observation period of at least 12 months from surgery (up to 20 months for several of the patients) 26 of the 39 followed up patients continued to have normal serum CEA levels; however, three of them showed recurrence of the tumor, either local (two patients, 18 and 20 months after surgery) or distant metasteses (one patient, 18 months after surgery). Whereas, 13 patients (33.3% of this group) showed a significant, progressive rise of their serum CEA titers up to pathologic levels, after periods ranging from 3 to 12 months from surgery (average 7.6 months);

subsequently, the serum CEA levels returned to normal in two of these patients, while being maintained at abnormal values in the remaining 11 patients. The stable serum CEA elevation in these 11 patients preceded clinical and/or laboratory findings of tumor recurrence (as judged by physical examination, recto-sigmoidoscopy, hematochemical tests, liver scan, bone scan, or chest X-ray) by an average period of 3–6 months (average 3.5 months) in nine of these patients. On the contrary, two of the 11 patients with stable serum CEA elevation continued to be free from any clinical and/or laboratory sign of tumor recurrence, respectively 3 and 7 months after the onset of serum CEA increase (15 and 13 months after surgery).

As to the 32 patients with elevated preoperative serum CEA in whom the CEA titers had returned to normal values after surgery, 12 of them (37.5%) showed a subsequent rise of serum CEA to abnormal values after periods ranging from 3–12 months after surgery. This serum CEA elevation preceded the clinical and/or laboratory evidence of tumor recurrence by an average period of 2–5 months in nine of the patients, while three patients continued to be free from other evidence of tumor recurrence 3–6 months after stable serum CEA elevation. There were not clinical and/or laboratory signs of tumor recurrence in the 20 patients in whom surgery had produced complete and long-lasting normalization of previously increased serum CEA values.

DISCUSSION

The results of clinical and laboratory follow-up and of serum CEA monitoring in the patients with positive preoperative values are in keeping with previous reports [(4, 5, 7–11, 16, 25)]. In fact, the reduction of serum CEA to normal levels observed in these patients as the result of surgery was followed in several of the patients (12 out of 32) by a subsequent, steady rise of the serum CEA titers, at time intervals ranging from 3 to 12 months after surgery. Clinical and laboratory work-up of these patients confirmed thereafter the recurrence of the tumor in nine of them, after an average period of 2–5 months after the detection of the serum CEA elevation, whereas three were the apparently false positive cases (at least until the time of last clinical and laboratory follow-up).

On the contrary, the results of serum CEA monitoring obtained in the patients with normal preoperative values deserve particular attention. In fact, a consistent proportion of these patients (11 out of 39, 28.2%) subsequently showed, at various times after surgery, a steady rise of their serum CEA titers, which was an early indicator of tumor recurrence in nine of them (i.e., in 81.8% of these cases). Thus, the pattern of this serum CEA positivity and of subsequent detection of tumor recurrence by other, independent means was approximately the same as for the patients with positive preoperative serum CEA in whom surgery had reduced the serum CEA levels to normal values. In fact, the serum CEA positivity rate during the follow-up period was 33.3% in the patients with negative, and 37.5% in those with positive preoperative serum CEA, while the apparent false positive cases were respectively 5.1 and 9.4%; the only remarkable difference between the two groups concerned the false negativity rate, which was 7.7% in the patients with normal preoperative serum CEA, while there were not false negative cases among the patients with positive preoperative serum CEA.

As to our knowledge, there are a few, scattered reports of occurrences like the ones just described in colorectal cancer patients with negative preoperative serum CEA, derivable only after a thorough analysis of the published studies [13, 15, 19–21]. As a matter of fact, the vast majority of the studies published so far deals with the follow-up of patients with positive preoperative serum CEA values, so much so that an elevated preoperative serum CEA value is often indicated as the main criterion for selecting the patients to be followed up with serial assays of their serum CEA levels as an early indicator of tumor recurrence [6, 7, 10, 15–18]. The rationale for excluding the patients with negative preoperative serum CEA values from this kind of follow-up is the alleged unlikelihood that such patients will subsequently develop high titers of serum CEA as a consequence of tumor recurrence. This conclusion appears to be contradicted by the results obtained in the present study which, though of a preliminary nature, indicate with a sufficient body of evidence that about one out of three patients with colorectal cancer and negative serum CEA preoperatively is expected to develop, in the first year or so after surgery, elevated CEA titers as an early indicator of tumor recurrence. This finding is in keeping with previous reports showing the poor correlation between tumor size and plasma CEA

concentrations [26, 27]; in this perspective, it may be assumed that the CEA serum levels depend on the secretion pattern rather than on the mass of the tumor, as different secretion patterns have been described [28]. This conclusion is further supported by the false negative results observed in three of our patients with normal preoperative serum CEA levels; in fact, it is unquestionable that these patients certainly had recurrent tumor, as proven by histology (extensive local recurrence in two cases, hepatic metastases in one case), yet their serum CEA levels continued to be completely normal. On the other hand, the general observation that recurrent tumor often produces elevated serum CEA levels, even though the primary tumor did not, has been recently mentioned [29]; thus, our results fully confirm and quantitate such observation, and lead to the conclusion that the CEA secretion pattern of the recurrent tumor may be different from that of the primary tumor.

The importance of finding a rising serum CEA titer in patients with colorectal carcinoma is obvious from the diagnostic point of view, whereas the practical implication of such finding as concerns treatment of the tumor, and eventually benefit to the patients, is not yet definitely proved. As a matter of fact, while the value of chemotherapy for such tumors is confined almost solely to 5-fluorouracil, studies are currently under way in order to assess the actual efficacy of second-look surgery in the treatment of colorectal cancer [12, 17, 21, 29, 30], also in view of the fact that most tumor repetitions appear to be confined to local recurrences in the pelvis [29].

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