Serum Sialyltransferase Levels as a Parameter in the Diagnosis and Follow-up of Gastrointestinal Tumors

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ABSTRACT

Serum sialyltransferase (SST) levels were determined in patients with various gastrointestinal cancers at different clinical stages. These SST values are significantly elevated over normal healthy controls, and a correlation was observed between tumor stage and SST activity. While SST levels rise in patients with increasing tumor burdens, they revert to normal in patients with undetectable tumor tissue after radical surgery.

INTRODUCTION

Reports of altered glycosyltransferase activities in malignant cells and tissues (1) had led us to examine the clinical applicability of SST³ determinations as an aid in the diagnosis of malignant disease. Previous results demonstrate that SST levels are elevated over those of normal healthy controls in approximately 80% of the patients suffering from various forms of malignant disease. The earlier results also show that SST data parallel the classical criteria used in therapeutic monitoring of tumor patients (2, 4, 5, 7, 8).

Presently, we report on the SST levels of patients suffering from gastrointestinal tumors of different clinical stages. The following interrelations were examined: (a) SST levels of patients with gastrointestinal cancers of different organ sites and clinical stages as compared to those of normal controls; (b) SST levels of patients with large-bowel carcinomas as allocated to Dukes' Stages A to D; (c) SST levels of patients with primary large-bowel cancers as compared to SST levels of patients with benign tumors of the large-bowel mucosa; (d) SST levels of patients after surgery for large-bowel carcinomas as related to the clinical course following surgery; and (e) SST levels of patients with large-bowel carcinomas as compared to CEA levels determined from the same patients.

MATERIALS AND METHODS

Subjects Tested. Normal controls were 84 healthy individuals with a male:female ratio of approximately 1:1 and an age range of 30 to 75 years. Patients were assigned to one of 4 groups: Group 1, patients with large-bowel cancer; Group 2, patients with other gastrointestinal cancers; Group 3, patients with benign tumors of the large-bowel mucosa; and Group 4, patients in disease-free intervals after surgery for large-bowel cancers. The clinical condition of each patient was designated in accordance with the criteria described in the International Union against Cancer report (10).

Patients with Large-Bowel Cancer (Group 1). This group consisted of 79 patients with carcinoma of the large-bowel mucosa. Thirty-one patients had primary disease with or without metastases to the regional lymph nodes (Dukes' A, 12; Dukes' B, 12; and Dukes' C, 7, and 6 had primary cancer with either hepatic or distant metastases (Dukes' D) at the time the blood sample was taken. In 65% of patients with primary cancer, the tumor was located in the rectum. Those patients with cancer of the colon had primary lesions at various sites with a high incidence at the sigmoid colon. With the exception of one patient who suffered from a squamous cell carcinoma of the anus, all tumors were adenocarcinomas with varying degrees of differentiation. Forty-two patients suffered from tumor relapse. Of these, 7 had local relapse, 15 had hepatic metastases, and 20 had distant metastases.

Patients with Other Gastrointestinal Cancers (Group 2). In this group, 10 patients had primary gastric cancer. One patient was assigned to Stage I, and 3 patients each were assigned to Stage II, III, and IV. Sixteen patients showed gastric tumor relapse postsurgery. Of these, 14 showed distant metastases. Nine patients had esophageal cancer, and 9 patients had pancreatic cancer. All patients with esophageal or pancreatic cancers showed distant metastases.

Patients with Benign Tumorous Lesions (Group 3). This group consisted of 8 patients who suffered from adenomatous polyps of the large-bowel mucosa. Each diagnosis was confirmed by histological examination of the lesion since X-ray examination or endoscopy had not given unambiguous results.

Patients in Disease-free Intervals after Surgery for Large-Bowel Cancers (Group 4). Of the 88 patients in this group, 35 reported for several examinations, whereas 53 reported for only a single examination.

Sialyltransferase Assay. Sialyltransferase was determined in serum samples by the use of the insoluble acceptor-complex method, whereby asialofetuin was covalently bound to cyano- gen bromide-activated Sepharose 4B (Pharmacia, Uppsala, Sweden) (4). A suspension of this insoluble acceptor in buffer was mixed with cytidine monophospho-N-[¹⁴C]acetylneuraminic acid (as sialyl donor) and the serum sample (as enzyme source). After incubation, the acceptor resin was washed several times to remove unbound radioactivity. Transferred radioactivity was calculated as milliunits SST per ml, whereby 1 unit of SST is the amount of enzyme which transfers 1 pmol [¹⁴C]-N-acetylneuraminic acid to the acceptor under the above-described conditions. The normal range (50.6 ± 12.1 milliunits SST per ml, mean ± S.D.) was calculated by testing sera from
normal controls. Enzyme levels above 74.8 milliunits SST per ml (mean ± 2 S.D.) were considered pathological. CEA levels were determined by the CEA Roche test (Onko-med Labor, Vienna, Austria).

RESULTS

Patients with Gastrointestinal Cancers of Different Organ Sites and Clinical Stages

The SST values of 123 patients with different gastrointestinal cancers (primary cancer or metastases, Patient Groups 1 and 2) are shown in Chart 1. These values were derived from blood samples taken at the first clinical examination. Of the patients in this group, 55.2% showed SST levels of 74.8 milliunits/ml (mean ± 2 S.D. of the normal controls) or greater, and were considered in the pathological range. The following correlations were found between enzyme levels and the individual patient’s clinical status. (a) Of the patients with primary cancer and distant metastases or with tumor burden, 75% were found to have SST values in the pathological range (>74.8 milliunits/ml). (b) Of the patients with small tumor masses (primary cancer with or without metastases to the regional lymph nodes, or local relapse), approximately 60% had SST values between 62.7 (mean ± 1 S.D.) and 74.8 milliunits/ml (mean ± 2 S.D.).

Patients with Large-Bowel Carcinomas of Dukes’ Stages A to D

The correlation between the clinical stage of disease and SST activity for 79 patients suffering from large-bowel cancer (Patient Group 1) is shown in Chart 2. In the absence of more suitable staging parameters, patients suffering from tumor relapse postsurgery were assigned to Dukes’ Groups C and D as follows. Depending on the tumor mass and metastatic involvement estimated by clinical examination, patients with metastases to the regional lymph nodes or solitary liver metastases were assigned to Dukes’ Group C, whereas patients with metastatic involvement beyond solitary liver metastases were assigned to Dukes’ Group D. Although not strictly in keeping with established classification procedures, these assignments appear justified in view of the correlation between SST values and tumor mass as documented previously for patients with mammary carcinomas (2). Statistical analysis (Table 1: Kruskal-Wallis test) shows that patients at all stages (Dukes’ A to D) have significantly elevated levels of SST relative to that of normal healthy subjects. There is no significant difference between the enzyme levels observed at Dukes’ Stages A to C, but these are quite distinct from SST levels at Dukes’ Stage D. This finding is due to the great variation of enzyme values seen in patients with Dukes’ Stage A. Among these, one patient had an abnormally high enzyme level (1 14 milliunits SST per ml). This patient suffered from a small area of malignant cells in a papillary adenoma with a diameter of 4 cm. Another patient at Dukes’ Stage A showed an enzyme level of 99 milliunits SST per ml and had a primary tumor of an undifferentiated adenocarcinoma type. This patient had a disease-free interval of approximately only 3 months after apparently all tumor had been surgically removed. The lowest enzyme level (32 milliunits SST per ml) was seen in a patient with a squamous cell carcinoma of the anus. All other patients with Dukes’ Stage A suffered from adenocarcinomas with tumor diameters of 2 to 4 cm. When the 3 extreme values mentioned above are not considered in the statistical analysis, a significant correlation between the Dukes’ stages and enzyme levels can be made. A similar correlation has been reported in patients with breast cancer or patients suffering from Hodgkin’s disease where larger, more homogeneous populations had been studied (2, 3, 7).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Dukes’ A</th>
<th>Dukes’ B</th>
<th>Dukes’ C</th>
<th>Dukes’ D</th>
</tr>
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<tr>
<td>Normal</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duke’s A</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duke’s B</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Duke’s C</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duke’s D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Classification of the extent of spread of operable carcinoma of the large intestine in surgical specimens.  
**NS, not significant.
Early Diagnosis of Gastrointestinal Cancers

In order to determine whether or not SST estimation could assist in the early diagnosis of gastrointestinal cancers, sera from 37 patients with large-bowel cancers and from 8 patients with benign tumorous lesions of the large-bowel mucosa were analyzed (Table 2; 37 from Patient Group 1 and all of Patient Group 3). There are no significant differences between enzyme levels estimated in patients with primary cancer in early stages (Dukes' A to C) and benign tumorous lesions.

Patients under Prolonged Observation (Follow-up)

The surgical removal of tumors causes a transient increase of enzyme activity in 70% of the cases examined followed by a significant decrease of enzyme activity within 4 weeks. The difference between the pre- and postoperative enzyme levels can be very large (up to 60 milliunits SST per ml), especially in cases where apparently all tumor tissue had been surgically removed. In most cases, after successful operation, SST levels revert to normal. In those patients with residual local tumors, the postsurgery values are also decreased but do not revert to normal and may be correlated with the remaining tumor mass. In contrast to observations with CEA, no correlation was seen between the postoperative decreases of SST levels and the incidence of relapse in radically operated patients (9, 11).

For detailed analysis of the data obtained during prolonged observation, the patients in this group were divided into 3 subgroups based on the clinical course of their disease.

Subgroup A contained 35 patients not suffering from relapse after apparently successful tumor removal. A total of 107 SST determinations was made. Each patient was checked 2 to 6 times (mean, 3) with a maximum period of 450 days (mean, 180.3 days) (Chart 3, left). Of these 107 tests, 92 were within the range of the mean + 1 S.D. (62.7 milliunits per ml), 12 were in the range 62.7 to 74.8 (mean + 1 S.D. to mean + 2 S.D.) milliunits/ml, and 3 exhibited SST levels above 74.8 milliunits/ml (mean + 2 S.D.). These 3 latter values were found in 3 different patients. One of these suffered from local inflammation in the area of the operation, another was found to have a benign rectal polyp which was subsequently removed, and the third was found to be symptom free. The values before and after this increase were in the normal range. The mean value of all SST activities was 54.1 milliunits/ml. Analogous to these results, 53 patients without relapse showed a mean SST value of 55.8 milliunits/ml based on one determination/patient. The statistical distribution of the enzyme values of these 2 groups was identical to that of the control group. Thus, after successful tumor removal without relapse, SST values revert to normal and remain in this range if no metastases develop.

Subgroup B is made up of 15 patients of Subgroup A who eventually suffered from progression of their conditions (Chart 3, right). Within the time of observation (mean, 69 days), 34 SST determinations were made. The initial value was taken at a time when no clinical signs of relapse were evident. The next determination was made when suspicion arose or clinical evidence was available that metastases had appeared. The statistical evaluation of the SST activities and the clinical course of the disease showed that the mean value of the SST initially was in the range of 51.1 ± 10 milliunits/ml and rose to 83.2 ± 12.2 milliunits/ml with the progression of disease. The change of the mean values is, therefore, 32.1 milliunits/ml and represents a statistically highly significant difference. For each group, patients without relapse and those with progression of disease, 2 distinct regression equations could readily be calculated. Thus, it may be concluded that the clinical course of the disease in an individual case is paralleled in a statistically highly significant manner by the SST enzyme activity.

In Subgroup C (patients with metastases), 17 patients were examined. All of these were under treatment with cytostatic drugs according to established regimens. Sixty-four SST determinations were performed on this group. Because of the small population size, a statistical analysis of the data was not feasible. Nevertheless, the majority of patients (78%) had SST values above 74.8 milliunits/ml.

Of the 17 patients with metastases, 5 suffered from colon cancer with progressive tumor growth even during therapy. The progression of the disease was closely correlated with increasing levels of SST activity. Most of the other patients were undergoing treatment of residual tumors following surgery. Chemotherapy was highly successful in 2 cases, and the degree of success was correlated with a decrease in SST enzyme activity. Other patients with constant conditions during the period of observation showed nearly constant enzyme activity values. Thus, the findings of Henderson and Kessel (6) in other cancer types were confirmed.

### Table 2

<table>
<thead>
<tr>
<th>SST values of patients with primary cancers and benign tumorous lesions</th>
<th>n</th>
<th>Mean ± S.D. (milliunits/ml)</th>
<th>Statistical analysis (2 x 2 contingency table)</th>
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</thead>
<tbody>
<tr>
<td>Large-bowel cancers Dukes A</td>
<td>12</td>
<td>64.6 ± 24.4</td>
<td>3/12</td>
</tr>
<tr>
<td>B</td>
<td>12</td>
<td>62.9 ± 15.5</td>
<td>3/12</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>68.9 ± 12.2</td>
<td>1/7</td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>108.8 ± 39.5</td>
<td>6/6</td>
</tr>
<tr>
<td>Benign tumorous lesions</td>
<td>8</td>
<td>63.8 ± 15.0</td>
<td>2/8</td>
</tr>
<tr>
<td>Normal healthy subjects</td>
<td>84</td>
<td>50.6 ± 12.1</td>
<td>2/84</td>
</tr>
</tbody>
</table>

<sup>a</sup> NS, not significant.
The Diagnostic Value of SST Determinations Related to CEA Tests at Different Clinical States

In order to assess the diagnostic value of SST in relation to that of CEA, 116 patients from Patient Groups 1 and 4 were studied. SST and CEA tests were performed on the same day. According to their clinical state, the patients were divided into 3 subgroups: (i) patients with primary cancer without liver metastases (Dukes' A to C); (ii) patients after successful operation without relapse; and (iii) patients with proven metastases. "Correct diagnosis" is defined as follows: for patients with proven tumor masses (primary cancer or metastases), the criterion is levels of CEA above 10 ng/mI and SST values above 74.8 milliunits/mI; for patients with undetectable tumor masses (without relapse after surgery), the criterion is SST levels below 10 ng/ml and CEA levels below 74.8 milliunits/ml. Using this set of criteria, a comparison was made between the results obtained with SST and CEA determinations (Table 3; Chart 4).

Primary Diagnosis of Patients in Subgroup i. Neither SST nor CEA determination could assist in the primary diagnosis of cancers (Dukes' A to C), and therefore, neither could appear to have diagnostic value or clinical application in this regard. Only 3 of 23 patients had elevated CEA and SST levels; 4 patients had enzyme levels of more than 74.8 milliunits SST per ml but CEA levels of less than 10 ng per ml. In 15 of 23 patients (65%), neither CEA nor SST levels were in the pathological range.

Patients in Subgroup ii after Surgical Tumor Removal Without Relapse. Both SST and CEA are of similar and greater diagnostic value in this group than in Group 1. Thus, in 43 of 53 patients, both parameters were below the pathological range and therefore gave the "correct diagnosis." The remaining patients showed randomly elevated or lowered levels of CEA or SST.

Patients in Subgroup iii after Surgical Tumor Removal with Relapse. In 70% of these cases, SST was elevated to 74.8 milliunits/ml or more in contrast to CEA where only 45% of these patients were in the pathological range. The incidence of cases where elevated SST levels corresponded to the progression of disease was significantly higher (p < 0.05) than was the incidence of cases where progression was paralleled by augmented levels of CEA.

DISCUSSION

SST determinations in patients with gastrointestinal cancers of different organ sites and clinical stages seem to indicate that the test is not helpful in a general cancer screen. Even of the patients with distant metastases, 25% had SST levels below the pathological limit of 74.8 milliunits/ml (mean of normal controls ± 2 S.D.). Sixty % of the patients with small tumor masses (primary cancer with or without metastases to the regional lymph nodes or local relapse) had SST levels between 62.7 and 74.8 milliunits/ml (i.e., levels which cannot be classified as pathological).

The comparison of Dukes' stages with SST levels in patients suffering from carcinomas of the large-bowel mucosa shows that the mean SST level in Dukes' D patients is 102 milliunits/ml and is thus distinct from the mean SST levels of Dukes' A to C patients (p < 0.001). This finding suggests the use of SST determinations to predict metastatic involvement when a primary tumor has been detected by X-ray or endoscopic examination.

A comparison of SST levels between patients with benign tumorous lesions of the large-bowel mucosa and patients with primary large-bowel cancers in early stages reveals no significant differences. Hence, the SST test cannot be used to indicate the transformation of, e.g., an adenomatous polyp to an adenocarcinoma.

In patients having undergone surgery for large-bowel carcinomas, SST determinations have proved to be reliable indicators of tumor removal, disease-free intervals, or relapse (see "Results"). The test also compares well with the CEA test in the cases studied and is superior to this assay with patients suffering relapse after surgical tumor removal. With patients under follow-up after surgical tumor removal, a rise in SST activity in the absence of other clinical signs is indicative of metastatic involvement or relapse and may be taken as a criterion for early initiation of systemic chemotherapy.

The inadequacies preventing the use of the SST assay in a wider context may well be due to the insufficient basic knowledge regarding SST in cancer patients. Thus, SST activities rather than SST concentrations are determined, and enzyme activities are potentially subject to changing influences of other serum components. It is hoped that methods for the determination of SST concentrations (such as radioimmune assays) will become available in the foreseeable future so that error margins will be considerably reduced. Furthermore, it remains unclear whether the elevated SST levels in cancer patients are due to augmented normal SST or to (an) isoenzyme(s) specific for malignant cells. Finally, it is unknown which property of a

Table 3

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>SST (milliunits/ml)</th>
<th>2 x 2 contingency table</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA (ng/ml)</td>
<td>&gt;74.8</td>
</tr>
<tr>
<td>Primary cancer (n = 23)</td>
<td>&gt;10</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>4</td>
</tr>
<tr>
<td>After surgical removal</td>
<td>&gt;10</td>
<td>13</td>
</tr>
<tr>
<td>With relapse (n = 40)</td>
<td>&lt;10</td>
<td>15</td>
</tr>
<tr>
<td>Without relapse (n = 53)</td>
<td>&gt;10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>5</td>
</tr>
</tbody>
</table>

* NS, not significant.

Chart 4. Correlation of SST values to CEA levels in different clinical conditions (a, patients with small primary cancers; b, patients with relapse or with large primary cancers; x, patients without relapse). mL, milliunits.

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tumor is reflected in or causes the elevation of SST activity. These questions being under active study by several groups of investigators, it is hoped that further developments in this area will provide the clinician with a versatile blood diagnostic test for malignant tumors of the gastrointestinal tract as well as other organ sites.

ACKNOWLEDGMENTS

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REFERENCES

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