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Carcinoembryonic Antigen and Humoral Antibody Response in Patients with Thyroid Carcinoma[1]

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SUMMARY

Carcinoembryonic antigen and antibodies to thyroglobulin and to a microsomal fraction of thyroid were measured. Persons examined were normal volunteers, patients with thyroid cancer, and patients with a history of childhood irradiation to the thymus and/or tonsil who were otherwise normal. Elevated antigen and antibodies were most frequently found in the cancer thyroid group. Thyroid cancer patients with no previous history of childhood irradiation were more frequently positive for antigen and antibodies than all other categories studied. Thyroid cancer patients with a previous history of childhood irradiation showed normal frequencies of antigen and antibodies. The results suggest that the antigenic expression and host response to the tumor in patients with thyroid cancer depend on its pathogenesis. Mention is made of similar findings in animal model systems.

INTRODUCTION

Elevated levels of circulating CEA[3] have been found in association with various cancers, especially those originating from the gastrointestinal tract (6, 13). Less frequently, elevated levels have also been obtained with certain nongastrointestinal cancers, such as those involving the breast, bronchus, and prostate (5, 9).

The only reported study of CEA levels in patients with thyroid disease that the authors are aware of is that of Laurence *et al.* (5). They studied 6 patients with nodular goiter, 2 with adenomata, and 1 with a carcinoma. None of their patients had elevated levels. The present investigation was undertaken to determine the usefulness of measuring circulating CEA in patients with thyroid cancer. Their humoral antibody response to a microsomal fraction (of thyroid) and to thyroglobulin was also examined. Irradiation to the thymus or tonsillar area in infancy has been shown to result in an increased incidence of subsequently developing thyroid cancer (4). Therefore, in this study, the results of assays on patients were analyzed to determine whether this factor (irradiation) had any influence on the data that were obtained.

MATERIALS AND METHODS

Controls. Twenty-nine subjects consisting of volunteer students and technicians, all nonsmokers, served as controls for the CEA assay. One hundred unselected preemployment personnel served as controls for the antibody tests.

Patients. In all, 237 patients were studied. Fifty-seven of these patients had thyroid cancer, of whom 26 had no previous history of childhood irradiation to the tonsil and/or thymic areas, and their mean age was 38.4 ± 14.7 years (S.D.). The remaining 31 thyroid cancer patients (mean age, 30.7 ± 10.1 years) had a history of childhood irradiation to the thymus or tonsil, and this was corroborated by a hospital record in 63% of cases. One hundred eighty patients, otherwise normal, but with a history of irradiation to the thymus or tonsil and who sought medical advice to exclude pathology, were studied; the history of 53% of these patients was corroborated by a hospital record.

A careful history was obtained and a full physical examination was carried out on all patients. Special investigations done included serum total thyroxine, radioactive iodine uptake, and thyroid scan.

The procedure for measuring CEA was that as described by Laurence *et al.* (5), which is a modification of the triple-isotope method of Egan *et al.* (3). (CEA and its antibody were gifts from Dr. Charles W. Todd, Department of Immunology, City of Hope National Medical Center, Duarte, California 91010.) In this assay system, levels greater than 12.5 ng/ml are considered abnormal, although not exclusively due to the presence of cancer.

Thyroglobulin antibodies were measured with the Thyroid Test Kit and microsomal antibodies were measured with the Microsome Test Kit, both obtained from Fujizoki Pharmaceutical Co., Ltd., Tokyo, Japan. A positive reaction at a serum dilution of 1:20 or greater was considered indicative of the presence of antibody.

RESULTS

Levels of circulating CEA in volunteers and patients are shown in Tables 1 and 4. Elevated CEA levels were found in 24% of noncancer patients with a history of childhood irradiation, compared to 10% for the control group. The increased frequency of elevated CEA levels in the noncancer

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[3] The abbreviation used is: CEA, carcinoembryonic antigen.

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patients is difficult to explain. One contributing factor may have been the inclusion of smokers or those who had smoked (40% of these patients), since moderate to heavy smoking is frequently associated with an elevated CEA level (10, 12), and this was also found in the present study. In the thyroid cancer group, 36% had elevated CEA levels. Analysis of the cancer patients showed 18% (3 of 17) of those with a previous history of irradiation to have an elevated CEA level; this compared with 56% (9 of 16) in the group of thyroid cancer patients with no known previous history of irradiation to the tonsil or thymus. Furthermore, in this latter group, when the CEA level was elevated, the concentration frequently tended to be higher (>20 ng/ml) than that in all other categories of patients. The results of examining volunteers and patients for thyroglobulin and microsomal antibodies are shown in Tables 2 to 4. Thyroglobulin antibodies were detected more frequently in patients with thyroid cancer and this was solely due to those without a history of irradiation exposure (Tables 2 and 4). Similarly, microsomal antibodies were more frequently detected in the thyroid cancer group and this also was solely due to those without a history of irradiation exposure (Tables 3 and 4).

No obvious relationship was found between the levels of CEA and the spread or grade of tumor involved. Similarly, the antibody titers did not correlate with the degree of tumor spread or differentiation.

DISCUSSION

CEA levels were more frequently elevated in noncancer patients than in control subjects. This may have been due to

Table 1

Circulating CEA levels (postoperative) in patients with cancer of the thyroid

	No. of subjects	No. of subjects with following CEA concentration			% positive	χ^2 test
		<12.5 ng/ml	12.5–20 ng/ml	>20 ng/ml		
Control group (students and technicians; nonsmokers)	29	26	3		10	
History of childhood irradiation to thymic or tonsillar region; examination revealed no obvious pathology	105	80	24	1	24	NS[a]
Carcinoma of the thyroid	33	21	9	3	36	$p < 0.02$
In patients with a previous history of childhood irradiation	17	14	3		18	NS
No previous history of irradiation	16	7	6	3	56	$p < 0.01$

[a] NS, not significant.

Table 2

Circulating thyroglobulin antibody levels (postoperative) in patients with cancer of the thyroid

	No. of subjects	Thyroglobulin antibodies				% positive	χ^2 test
		Not detected	Detected				
			Titer	No. positive			
Unselected preemployment personnel	100			3		3	
History of childhood irradiation to thymic or tonsillar region; examination revealed no obvious pathology	119	110	1/20	4	9	8	NS[a]
			1/40	2			
			1/80	2			
			1/320	1			
Cancer of the thyroid	51	44		7		14	$p < 0.02$
In patients with a previous history of childhood irradiation	31	30	1/20	1		3	NS
No previous history of childhood irradiation	20	14	1/20	2	6	30	$p < 0.01$
			1/40	2			
			1/160	1			
			1/640	1			

[a] NS, not significant.

Table 3
Circulating microsomal antibody levels (postoperative) in patients with cancer of the thyroid

		Microsomal antibodies				
			Detected			
	No. of subjects	Not detected	Titer	No. positive	% positive	χ^2 test
Unselected preemployment personnel	100			10	10	
History of childhood irradiation to thymic or tonsilar region examination revealed no obvious pathology	111	92	1/20 1/320 1/640 1/1,280 1/2,560 1/10,240	3 1 3 7 3 2 } 19	17	NS[a]
Cancer of the thyroid	37	29		8	22	$p < 0.10$
In patients with a previous history of childhood irradiation	18	16	1/80 1/160	1 1 } 2	11	NS
No previous history of childhood irradiation	19	13	1/80 1/320 Not titrated	3 2 1 } 6	32	$p < 0.02$

[a] NS, not significant.

Table 4
Antigen and antibody in thyroid cancer patients

	Patients with no previous history of childhood irradiation		Patients with a previous history of childhood irradiation		
Antigen or antibody	No. of patients	% positive	No. of patients	% positive	χ^2 test
CEA	16	56	17	18	$p < 0.05$
Thyroglobulin antibodies	20	30	31	3	$p < 0.01$
Microsomal antibodies	19	32	18	11	NS

the contribution of patients with smoking habits, many of whom had CEA levels in the range of 12 to 20 ng/ml. Patients with a history of irradiation to the tonsil or thymic area with or without thyroid cancer had comparable levels of CEA (18 and 24%). In contrast, thyroid cancer patients without a previous history of childhood irradiation had more frequently an associated elevation in the CEA (56% positive). This finding is consistent with the results of other investigators who studied transplantation antigens. Unlike the tumor transplantation antigens, CEA is not immunogenic in the autochthonous host. Nevertheless, present evidence suggests that CEA, α-fetoprotein, and the chemically induced cancer transplantation antigens are all embryonic in origin, being reexpressed with tumorigenesis (1). Moore and Williams (8) have demonstrated that most murine irradiation-induced osteosarcomata have a paucity of tumor-specific cell surface antigens. Furthermore, they found that osteosarcomata induced by a chemical carcinogen differs significantly in antigenic strength from those induced by irradiation (^{32}P), and concluded that, in these contrasting models of bone oncogenesis, antigenicity was more a function of the carcinogenic agent than the site of tumor origin. Similarly, Stjernswärd (11) found that irradiation-induced osteosarcomata was associated with a lower degree of antigenicity, compared with some (but not all) osteosarcomata induced by chemical carcinogens. Baldwin *et al.* (1) also reached a similar conclusion when studying irradiation- and chemically induced osteosarcomata.

A positive correlation has been found between the spread of tumor in cancer of the colon and CEA levels (13). However, in the present study no such relationship could be found. Published reports are not consistent regarding a relationship between the degree of tumor differentiation and CEA levels. Denk *et al.* (2) found that the more differentiated tumors had a greater abundance of CEA. In contrast, Martin and Martin (7) found no obvious correlation. Both studies were concerned with gastrointestinal cancer. In the present investigation, there was no evidence of CEA levels being related to the degree of tumor differentiation. The types of tumor present (not shown) in both groups of thyroid patients were essentially similar; almost all were of the well-differentiated type. There was no correlation of age with the CEA level, and this confirms the results of previous reports.

In addition to the findings in this study of an association of thyroid cancer with CEA levels, a similar tendency was also noted in the antibody studies. Those thyroid cancer patients without a history of irradiation to the thymus or tonsil more frequently were found to have antibodies directed against thyroglobulin and to a lesser extent against the microsomal fraction of thyroid (Tables 3 and 4). These findings are consistent with studies in laboratory animals; Stjernswärd (11) found the antibody response to an injected antigen (sheep red blood cells) to be generally less in irradiation-induced osteosarcomata than that induced by a chemical carcinogen.

The present study is in accord with the findings in experimental model systems and suggests that antigenic expression and host response to the tumor in patients with thyroid cancer depend on its pathogenesis.

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