Carcinoembryonic antigen in thyroid disease

J. ECONOMIDOU, P. KARACOULIS, O. N. MANOUSOS, E. MANESIS, A. KYDONAKIS, AND D. A. KOUTRAS

From the Second Department of Medicine, Hippokration Hospital, University of Athens, and the Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, Athens, Greece

SUMMARY Plasma carcinoembryonic antigen (CEA) levels were measured by the Z-Gel technique in 138 patients with benign thyroidopathies, 25 patients with thyroid cancer, and 141 normal persons. Levels were raised (above 5 ng/ml) in 2% of the normal subjects, in none of the patients with benign thyroidopathies, and in 20% of the patients with thyroid cancer. They were considerably raised in all cases of medullary carcinoma of the thyroid but they were also high in other histological types of thyroid cancer. Measurement of plasma CEA may be of value in the preoperative diagnosis and follow-up of patients with thyroid cancer.

Carcinoembryonic antigen (CEA), described by Gold and Freedman (1965), is a tumour-associated antigen which may be of value in the diagnosis of carcinoma of the colon and rectum and in the detection of recurrence after resection (Thomson *et al.*, 1969; Dahr *et al.*, 1972; Mach *et al.*, 1974). Raised plasma levels of CEA have also been reported in a variety of other neoplastic and inflammatory diseases (Lawrence and Neville, 1972). In view of the difficulties of diagnosing thyroid cancer preoperatively (British Medical Journal, 1976) we decided to explore the value of radioimmunoassay of CEA levels in the diagnosis of this disease. For purposes of comparison a number of non-malignant thyroidopathies were included in the study.

Patients and methods

A total of 163 patients with thyroid disease were studied together with 141 healthy persons (volunteer blood donors) as controls. In all patients the thyroid gland was carefully palpated. Symptoms and signs suggestive of hyperthyroidism were assessed by the criteria of Crooks *et al.* (1959). In all the patients a thyroidal ^{131}I uptake at 4 and 24 hours, a protein bound ^{131}I determination at 48 hours, and a thyroid scintigram were performed, as described by Malamou *et al.* (1959), together, when necessary, with other tests such as the T_3 suppression test, estimations of the serum T_4 and RT_3U , the TRH test, etc. The patients with evidence of thyroid tumour (nodules) were operated upon and the eventual diagnosis was

made on histological examination.

According to clinical, laboratory, and histological findings the patients were classified in the following groups: (a) non-toxic goitre, (b) benign 'cold' nodules, (c) Graves's disease, (d) toxic adenoma, (e) thyroid cancer, and (f) other thyroidopathies (Table 1). Plasma CEA was measured by radioimmunoassay using the Z-Gel technique (Hansen *et al.*, 1971; Lo Gerfo *et al.*, 1971). By this method the normal level is 2.5 ng/ml but higher levels may occasionally be found in apparently healthy people and patients with inflammatory diseases. Therefore 5 ng/ml is now considered a safer upper normal limit and we adhered to this in analysing our results.

Results

CEA levels in the various thyroidopathies and in the normal controls are shown in Table 1. In a small percentage of all groups studied levels between 2.5 and 5 ng/ml were found. Raised levels (above 5 ng/ml) were seen in 2.1% of the normal controls and in 20% of the patients with thyroid cancer. None of the patients with various types of benign thyroidopathies had raised levels.

Table 2 shows the histological type of the cases of benign 'cold' nodules. CEA levels between 2.5 and 5 ng/ml were seen in three of the 16 cases with colloid goitre whereas in all other cases levels were less than 2.5 ng/ml.

In none of the 25 cases of thyroid cancer was there any relationship between a raised CEA level and the presence of metastases. Also there was no correlation between the length of history of thyroid disease and

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Table 1 CEA levels in various thyroidopathies and in normal subjects

Diagnosis	Plasma CEA (ng/ml)				Incidence of levels >5 ng/ml (%)
	<2.5	<5	<10	>10	
Normal controls	134	4	2	1	2.1
Non-toxic goitre	34	2	—	—	—
Benign 'cold' nodules	46	3	—	—	—
Graves' disease	26	1	—	—	—
Toxic adenoma	21	—	—	—	—
Thyroid cancer	18	2	1	4	2.0
Others*	5	—	—	—	—

*De Quervain thyroiditis (1), Hashimoto thyroiditis (1), cyst of thyroglossal duct (3).

Table 2 Histological classification of benign 'cold' nodules

Histological type	No. of cases	Plasma CEA (ng/ml)	
		<2.5	<5.0
Follicular adenoma	29	29	—
Hurthle cell adenoma	2	2	—
Colloid goitre	16	13	3
Haemorrhagic cyst	2	2	—

CEA levels. The histological type of the malignant tumours in relation to CEA levels is shown in the Figure. CEA levels were raised in two cases of papillary and three cases of medullary carcinoma. That all three cases of medullary carcinoma had levels above 25 ng/ml is interesting.

Discussion

The human thyroid is endoderally derived and therefore inflammatory or hyperplastic lesions of it might be expected to be associated with raised plasma levels of CEA—as often happens with diseases of the gastrointestinal tract. Our study showed that CEA levels in patients with benign thyroidopathies were not raised relative to those in normal people. The lowest levels were seen in cases of hyperthyroidism, and this may be due to the increased catabolic state of the patients. In contrast to cases of benign cold nodules of the thyroid, in all of which levels were below 5 ng/ml, in 20% of the cases of thyroid cancer CEA levels were raised. In all cases of medullary carcinoma CEA levels were greatly raised (above 25 ng/ml). In two of the 13 cases of papillary carcinoma levels were also raised but they were not raised in the cases of follicular or undifferentiated (anaplastic) carcinoma.

Early studies of CEA included sporadic cases of thyroid cancer in various unselected series (Laurence *et al.*, 1972; Lo Gerfo *et al.*, 1972; Reynoso *et al.*, 1972; Papachristou *et al.*, 1973). Moreover, two recent reports give data on CEA in a larger series of

Figure Plasma CEA levels in various histological types of thyroid carcinoma. Open circles indicate metastatic disease and closed circles localized disease.

cases with cancer of the thyroid. Rochman *et al.* (1975), using the method of Laurence *et al.* (1972), investigated two groups of patients with thyroid cancer and found raised CEA levels in 24% of those with a past history of neck irradiation and in 56% of those without irradiation. However, CEA levels were not related to the degree of tumour differentiation, and the authors make no special comment on the histology of the tumours. Ishikawa and Hamada (1976), using a similar method, found raised CEA levels in all 13 of their cases of medullary carcinoma but in the other histological types of thyroid cancer the levels were within normal range.

The combined data of our study and that of Ishikawa and Hamada (1976) show that all cases with medullary carcinoma reported so far have markedly raised plasma CEA levels. This seems to be a specific product of the tumour cells (Isaacson and Judd, 1976). However, a study of a larger number of cases is required to confirm these observations. Medullary carcinoma is known to be a functional tumour with distinct histopathological features, secreting in addition to calcitonin substances such as ACTH, serotonin, histamine, and prostaglandins (Williams and Brewer, 1969). The active production of CEA by this tumour may be related to the overall hyperactive state of the neoplastic cells or to the distinct origin of the tumour cell, which is thought to be from the neural crest. It is of interest that high CEA levels are found in nearly all cases of neuroblastoma—another tumour of neural crest origin (Reynoso *et al.*, 1972).

The association of medullary carcinoma with CEA provides a new laboratory method which may be useful in the diagnosis and management of this type of cancer. Nevertheless, our own observations and those of Rochman *et al.* (1975) show that many patients with a non-medullary type of thyroid cancer may have raised CEA levels. Our findings support the view that the CEA radioimmunoassay may be of value in the diagnosis and postoperative follow-up of

patients with various types of thyroid cancer. The finding of low CEA levels in benign thyroidopathies adds to the eventual usefulness of the test.

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