Five Patients with Medullary Thyroid Carcinoma Presenting as Asymptomatic Elevation of Carcinoembryonic Antigen Level

Dear Editor,

Early detection of malignancies is not easy. Few methods of health screening have been proven to be of value. The use of carcinoembryonic antigen (CEA) in health screening has never been proven to result in early detection of cancers[1] but requests to test tumour markers continue to be made.

A raised CEA is not an uncommon finding and there are no established protocols on how to approach this issue. We report 5 cases where a raised CEA was the initial finding that later led to the diagnosis of medullary thyroid carcinoma (MTC).

Summary of the Five Patients

The patients (3 males and 2 females) ranged in age from 36 to 52 years at the time of presentation (Table 1). All had presented for a general health screen, which revealed no significant pathology apart from a raised CEA. None were smokers. The time from presentation to diagnosis of MTC ranged from 19 months (Patients 1 and 3) to 8 years (Patients 2 and 4) and 9 years (Patient 5).

The CEA level at presentation ranged from 5.5 to 58 ug/L. All the patients were referred for endoscopy within 1 month except for 1 (Patient 5, whose CEA was only 5.5 ug/L). This last patient had a mild elevation of CEA and the CEA even returned to normal before rising again gradually over a period of 3 years. After 3 years, Patient 5's CEA rose to 9.98 ug/L and she was referred for endoscopy.

All the patients (except Patient 1) had a repeat endoscopy as their CEA remained elevated without any clear cause established. Patients 2 and 4 had many endoscopic procedures performed yearly over a period of 8 years (until the diagnosis of MTC was made).

Three patients had a computed tomography (CT) scan of the thorax and abdomen within 3 months of presentation and in 1 patient (Patient 1), a thyroid nodule was detected. This was further investigated but the needle biopsy of the thyroid nodule was reported as a colloid nodule. Patient 3 had a second CT scan 17 months after presentation and this detected thyroid nodule (which was biopsied) was found to be positive for MTC.

Table 1. Summary of Patient Characteristics and Investigation Results

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Female	Male	Female
Age at presentation	52	38	48	44	36
Smoker	Previous	Previous	No	No	No
Initial CEA (ug/L)	58	Not known	6.5	38	5.5
Colonoscopy, time from presentation	Yes, 1 month	Yes, 1 month	Yes, 1 month	Yes, 1 month	Yes, 3 years
Repeat colonoscopy, time from presentation	No	Yes, 1 – 2 yearly after presentation	Yes, 1 year	Yes, Once yearly after presentation	Yes, 5 years
CT scan, time from presentation, thyroid nodule detected	Yes, 3 months, Yes	No	Yes, 1 month, No	No	Yes, 1 month, No
Repeat CT scan, time from presentation, thyroid nodule detected	No	No	Yes, 17 months, Yes	No	No
PET scan, time from presentation, thyroid nodule detected	Yes, 4 months, Yes SUV 2.5	Yes, 4 years, Yes SUV 2.8	No	Yes, 6 years, No	Yes, 3 years, Yes SUV 1.8
Repeat PET scan, time from presentation, thyroid nodule detected	No	Yes, 8 years, Yes SUV 3.2	No	Yes, 8 years, Yes SUV 3.5	Yes, 9 years, Yes SUV 2.8
Thyroid FNAC	Yes, benign	Yes, medullary carcinoma of thyroid	Yes, medullary carcinoma of thyroid	Yes, atypical cells	No
Time to final diagnosis	19 months	8 years	19 months	8 years	9 years
Size of tumour	2 cm	2.8 cm	1 cm	2 cm	1.5 cm

CEA: Carcinoembryonic antigen; CT: Computerised tomography; FNAC: Fine-needle aspiration cytology; PET: Positron emission tomography

Four patients (except Patient 3) had a positron emission tomography (PET) scan. In 3 of these patients, a thyroid nodule with focal uptake of fluorodeoxyglucose (FDG) was detected but SUV was in the low or equivocal range. Only Patient 1 proceeded to surgery after PET scan. The other 2 (Patients 2 and 5) continued to be observed and only when a second PET scan noted an increase in SUV of the thyroid nodule was biopsy or surgery performed. Patient 4 had thyroid nodule noted only in the second PET scan and this led to biopsy and later surgery of the thyroid nodule.

At the diagnosis of MTC, the size of tumour ranged from 1 cm to 2.8 cm. All the patients were negative for RET oncogene mutation. CEA levels returned to normal for 4 out of the 5 patients. Patient 5 had a persistently elevated CEA and is being further evaluated for malignancy.

Discussion

Carcinoma of the colon is a well-known cause for elevation of the CEA and invariably all these patients are referred for endoscopy. Lim YK in 2009, reported that out of 217 asymptomatic patients with raised CEA, a total of 20 patients were found to have primary and 8 to have metastatic cancers.[2] Of the 20 cases with primary cancers, only 11 were colonic cancers. The level of CEA was not found to correlate with the likelihood of detecting a malignancy in that study.

CEA can be raised in many malignancies apart from colonic cancer and also in benign tumours as well as other conditions like infections. CEA is often raised in smokers up to 2 times the upper normal range.[3]

The detection of incidental thyroid nodule on PET scan is not uncommon and estimated by Bertagna to be 2.46% of which malignancy occurred in 34.6% of those with focal hypermetabolic activity.[4]

Nodules that have diffused hypermetabolic activity were less likely to have malignancy (4.4%) in comparison with nodules that had focal hypermetabolic activity (34.8%).[5] Soelberg further reported that the SUV max was 4.8 for benign nodules as compared to 6.9 for malignant ones. The doctors investigating Patients 2 and 5 may have considered the nodule an incidental benign nodule and did not investigate further. Subsequently, Patient 2 had a repeat PET scan which showed that the nodule had increased in size and SUV max rose to 3.5. SUV max does not discriminate well between benign and malignant thyroid nodules and with hindsight thyroid biopsy should be done when there is a thyroid nodule and elevated CEA.

Our cases demonstrated that although there was a difference between malignant SUV max and benign SUV max (e.g. 7.04 versus 3.85 in Boeckman's study),[6] it is not sufficient to depend on this method to know whether a nodule is malignant. The thyroid nodules discovered on PET scan with focal uptake in Patients 2 and 5 should have been evaluated by ultrasound and fine needle aspiration.

Conclusion

The sequence of investigations and the time frame of investigations of these 5 patients demonstrate a high degree of variation. Different doctors appear to investigate this problem differently. All considered endoscopy within a short time of presentation but had different thresholds to ordering CT or PET scans.

In a patient with persistently elevated CEA, after negative endoscopy, CT scan or PET scan should be considered. If an incidental thyroid nodule is discovered, this should be further evaluated with a fine needle aspiration for cytology.

MTC is a relatively uncommon thyroid cancer forming about 4% of all thyroid cancers.[7] MTC is an established cause of CEA elevation and has been previously reported[8,9] but not all practitioners may be aware of this. This could have led to some delay in the diagnosis. In spite of the long delay of about 8 to 9 years in Patients 2, 4 and 5, the tumour was still confined to the thyroid with no lymph node involvement. Patient 5 still has an elevated CEA of uncertain aetiology but Cases 2 and 4 suggest a possibility that these tumours may be incidental and may not be as clinically significant as medullary carcinoma detected in other clinical settings.

Awareness and a high degree of suspicion is required in order not to miss an uncommon cancer like MTC.

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