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Case Report

A High Level of Carcinoembryonic Antigen as Initial Manifestation of Medullary Thyroid Carcinoma in a Patient With Subclinical Hyperthyroidism

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Carcinoembryonic antigen (CEA), a tumor marker with a glycoprotein structure, is frequently used in follow-up gastrointestinal malignancies. CEA levels may also increase in neuroendocrine tumors, including medullary thyroid carcinoma (MTC), and in some benign diseases. Patients whose blood tests show high CEA levels should have additional tests regarding MTC. Although MTC comprises only 3%–11% of all thyroid cancers, it should be tested because it has a poor prognosis and may accompany multiple endocrine neoplasia. We present the case of a 76-year-old man with subclinical hyperthyroidism with sporadic MTC who presented with initial high serum CEA levels. He underwent total thyroidectomy and left modified neck dissection. Pathologic specimens stained strongly for CEA. The patient's blood was analyzed for mutations in exons 10, 11, 13, 14, 15, and 16, but the RET proto-oncogene revealed no mutations. The patient was regularly followed by measurement of serum CEA levels and performance of positron emission tomography–computed tomography. Seventeen months after surgery, the patient has remained well and showed no signs of tumor recurrence.

Key words: MTC – CEA – PET-CT – MEN-II – RET proto-oncogene

Thyroid cancer (TC) is the most common endocrine neoplasm. Approximately 12,000 new cases of thyroid carcinoma are diagnosed annually in the United States, and an estimated 1000 deaths are caused by this disease each year.[1] Approximately 90% of thyroid carcinomas originating from the follicular epithelium are represented by well-differentiated tumors with papillary or follicular histotypes,[2,3] and 3%–11% of all thyroid carcinomas are represented by medullary thyroid carcinoma (MTC).[4–10]

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Hyperthyroidism, defined as hyperfunction of the thyroid gland, is diagnosed by clinical findings, laboratory findings, or both. Graves' disease is the most common form of hyperthyroidism, and a less common form of hyperthyroidism is uninodular or multinodular toxic goiter.[1]

The coexistence of hyperthyroidism and TC is extremely variable and may have distinct causes. The association of hyperthyroidism with differentiated TC has been extensively described, whereas its coexistence with MTC is very rare and usually diagnosed incidentally by histopathologic examination during or after surgery.[1,6] Only a few cases have been reported in the English language literature through April 2011.[4–7,11–16] We describe a patient who had MTC together with subclinical hyperthyroidism incidentally detected by a high level of carcinoembryonic antigen (CEA).

Case Report

A 76-year-old man presented to us with a complaint of reflux. His medical history involved a high blood CEA level as well as weight loss and fatigue for 6 months. He was thought to have a gastrointestinal malignancy and therefore underwent panendoscopy, colonoscopy, and contrast-enhanced abdominal computed tomography (CT). No pathology was detected other than reflux esophagitis. Blood pressure was measured at 140/80 mmHg, and his pulse rate was 98 beats/min. He appeared cachectic. A 3- to 4-cm mass was detected in the left side of his neck by deep palpation during the physical examination. The laboratory examination revealed the following: thyroid-stimulating hormone = 0.01 (0.2–4.2 μIU/mL), free triiodothyronine = 3.3 (3.1–6.8 pmol/L), free thyroxine = 18.2 (12–22 pmol/L), total thyroxine = 107.1 (66–181 nmol/L), total triiodothyronine = 1.43 (1.3–3.1 nmol/L), CEA = 386 (0–5.2 ng/mL), and calcitonin = 10.5 (<10 pg/mL). The patient had a normal serum calcium, parathormone, and 24-hour urinary excretion of metanephrines and vanillylmandelic acid. On ultrasonography, the right thyroid lobe appeared normal, whereas an approximately 6-cm nodule almost completely filled the left lobe together with a few 2- to 4-cm lymph nodes in the left cervical area. No pathology was detected in the surrenal glands with an abdominal CT. Marked contrast retention was observed in the left thyroid lobe and left cervical chain, suggesting malignancy with positron emission tomography–CT (PET-CT) (Fig. 1). The patient was given propylthiouracil for 3 weeks. Examination findings, thyroid function tests, PET-CT findings, and a high CEA level led to our initial diagnosis of MTC. MTC was suspected to be present during surgery because large, amphophilic cytoplasmic cells forming large clusters and separated from each other by fibrous bands with prominent boundaries were detected in frozen analysis of the left lobe. Bilateral total thyroidectomy plus left modified neck dissection was applied. A histopathologic examination showed a 5.5- × 3.5-cm partially encapsulated nodule in the left lobe with angiolymphatic and capsular invasion and positive amyloid deposits, which are histologic findings suggestive of MTC (Fig. 2). Two of the 10 lymph nodes removed were positive for MTC metastasis. Pathologic specimens stained strongly for CEA immunhistochemical stain (Fig. 3). CEA and calcitonin levels remained close to normal limits, and no relapse was observed radiologically (PET-CT) during the 17-month follow-up. No mutation of the RET proto-oncogene was detected in exons 10, 11, 13, 14, 15, and 16 in the patient's blood.

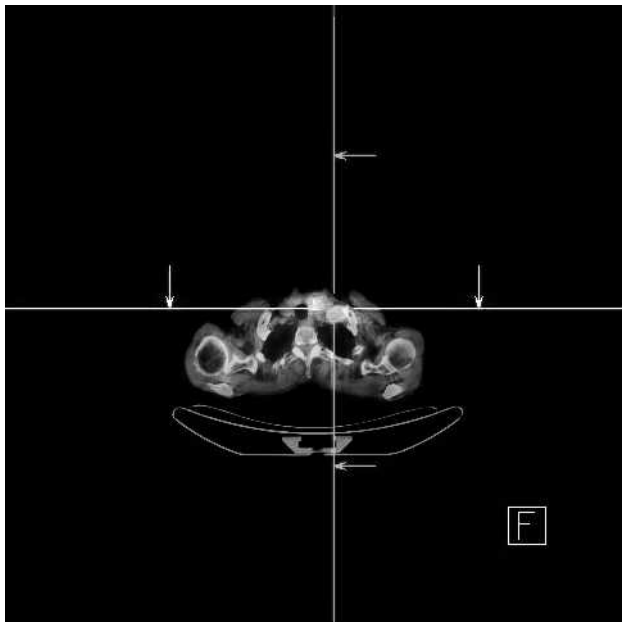

Fig. 1 The FDG-PET scan detected a left-sided thyroid nodule and a metastatic lesion in the left cervical region.

Discussion

Jaquet first reported MTC as ''malignant goiter with amyloid.''[17] Hazard *et al.*[18] provided a definitive histologic description in 1959, whereas Williams further stated that MTC originated from the calcitonin-secreting parafollicular C cells of the thyroid

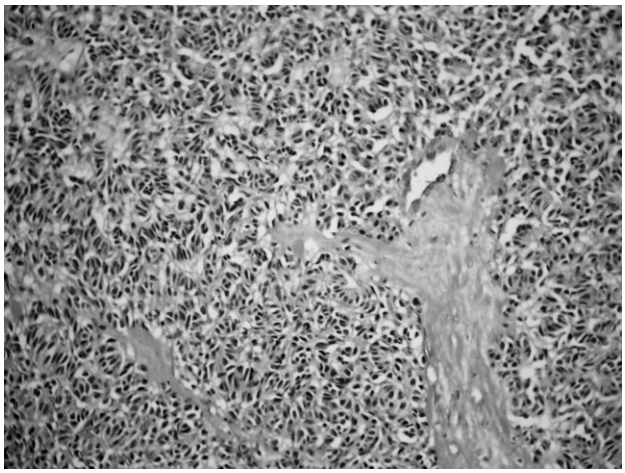

Fig. 2 Medullary carcinoma. Low power microscopic view showing a solid pattern of growth and deposition of amyloid (×100, H&E).

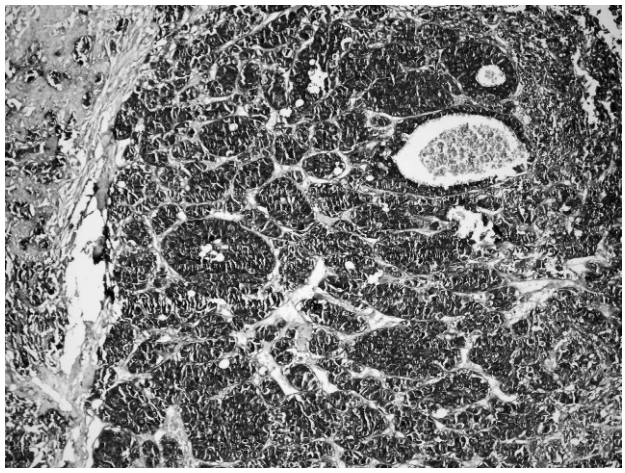

Fig. 3 Medullary carcinoma showing immunohistochemical positivity for CEA (×100, CEA stain).

and may occur in sporadic (75%) or hereditary (25%) forms.[3,5,10,19,20] The sporadic form usually presents with a palpable nodule or cervical lymphadenopathy, by which time basal calcitonin levels are almost always elevated.[20] Hereditary MTC is associated with a germ line mutation in the RET proto-oncogene and occurs either as isolated familial MTC or as part of multiple endocrine neoplasia type 2.[3,10,19] The patient in the present study had the sporadic form and it appeared as a palpable mass.

The frequency of thyroid malignancy in patients with hyperthyroidism varies from 0–21%.[2,4,11,12] In a literature search that we conducted using PubMed and Google Scholar databases from 1982–2010, we retrospectively evaluated a total of 36 articles in which 23,080 patients were presented. We concluded from these studies that different histologic types of TC accompanied hyperthyroidism in 3.2% (737 cases) of all patients. Papillary carcinoma was the most frequently reported histologic type, followed by follicular thyroid carcinoma.[4–7,11–16] The coexistence of MTC with hyperthyroidism is very rare. In addition, MTC accompanying hyperthyroidism was reported in a total of 20 patients in our literature search. We summarized the data of 15 patients of those presented in these studies in Table 1.[4–7,11–16,21,22]

Studies in this field suggest that MTC comprises 3%–11% of all TC.[3–10] Of the 737 TC cases we detected in our literature search, 20 (2.7%) were MTC. This study shows that hyperthyroidism does not cause a marked increase in any TC type.

MTC produces many tumor markers, including calcitonin, CEA, and chromogranin A. These markers can easily be detected with blood levels and immunohistochemical stains. Calcitonin is a hormone that is produced and secreted by thyroid C cells. Serum calcitonin levels are a highly sensitive tumor biomarker and considered to be 100% predictive of MTC when basal levels are >100 pg/mL or when stimulated levels with pentagastrin increase to >1000 pg/mL.[16] Therefore, these levels are useful tools for preoperative diagnosis and postoperative surveillance of disease recurrence. As in our patient, several cases in which calcitonin levels did not or mildly increased have been reported in literature. At present, only six cases have been reported of negative calcitonin or a lack of elevated MTC.[8–10,20,23] The demographic features of these patients are summarized in Table 2. The inability to monitor postoperative relapses by calcitonin levels in these cases causes difficulties in follow-up.

CEA is a glycoprotein that was first detected by Gold *et al* in 1965 in colonic cancer tissue.[24] CEA, mainly a tumor marker of gastrointestinal malignant diseases, is frequently used for follow-up of relapses and metastases. Tumors originating in the gastrointestinal system should be excluded first using endoscopy, colonoscopy, and CT in patients in whom high CEA levels are detected without any other clinical findings.[25] However, one should keep in mind that CEA is not a marker for only the gastrointestinal system and levels may increase in the course of some benign diseases, including liver cirrhosis and inflammatory bowel diseases, as well

Table 1 A summary of 15 cases of concomitant MTC in patients with hyperthyroidism reported in the English medical literature from 1980 to 2008

References	Year	Age	Sex	Thyroid disease	Calcitonin (pg/mL)	CEA (ng/mL)	FNAC	Tumor size (mm)	Presentation of MTC	Surgical Procedure	Follow-up time	Recurrence	Type of MTC
McFarland	1980	30	F	Graves	UN	UN	UN	12	Incidental	STT	UN	UN	Sporadic
Rieger	1989	61	M	Toxic MNG	UN	UN	(+)	T1	Cold nodule				
		67	F	Toxic MNG	UN	UN	(+)	T1	Cold nodule				
Schwartz	1989	40	F	Graves	UN	UN	UN	5	Incidental				
Small	1997	44	M	Toxic MNG	UN	UN	UN	UN	Incidental	TT	3 yr	No	Sporadic
Ruggieri	1999	72	F	Toxic MNG	UN	UN	UN	12.1		TT	9		
Brandle	1999	50	M	Graves	4572	UN	(+)	10	Diarrhea+ goiter	TT+BND	4 mo	No	Sporadic
		33	F	Graves	1300	UN	(+)	14	Cold nodule	TT+UND	4 mo	No	Sporadic
Angusti	2000	60	M	Toxic MNG	UN	UN				NP	Dead		UN
Mazzioti	2001	30	F	Graves	5125	55	(+)	16	Palpable nodule	TT+BND	12 mo	No	Sporadic
Nakamura	2002	32	F	Graves	110	1.4	UN	3.5	Incidental	STT	28 mo	No	Sporadic
Habra	2004	70	M	Graves	18,300	36.4	(+)	11	Palpable nodule	TT	UN	Yes	Sporadic
Michalek	2005	40	F	Toxic MNG	UN	UN	(+)	UN	Palpable nodule	TT+UND	UN	UN	UN
Cerci	2007	UN	F	Toxic MNG	UN	UN	(−)	5	UN	TT			
Phitayakorn	2008	54	F	Toxic MNG	UN	UN	UN	21	UN	UN	UN	UN	UN
Present study	2010	76	M	Toxic SN	10.5	386	NP		Incidental+ goiter	TT+UND	10 mo	No	Sporadic

BND, bilateral node dissection; CEA, carcinoembryonic antigen; FNAC, fine needle aspiration cytology; MNG, multinodulary goiter; MTC, medullary thyroid carcinoma; NP, not performed; SN, solitary nodule; STT, subtotal thyroidectomy; TT, total thyroidectomy; UN, unnoted; UND, unilateral node dissection.

Table 2 A summary of the 6 cases with normal levels or lack of marked elevation of calcitonin in patients with MTC reported in the English medical literature from 2000 to 2010

Reference	Year	Age	Sex	Presentation	CT (pg/mL)	CEA (ng/mL)	FNAC	Frozen section	Tumor size (mm)	Surgical procedure	RET mutation	Immunohistochemical stain			
												CT	CEA	CGA	SPH
Redding	2000	30	F	Palpable nodule	28 (25–150)	0.5	Malignant	ND	45	TT+BLND	Negative	(+)	(+)	(−)	(+)
Diez	2004	65	F	Goiter	N	N	Malignant	UN	UN	UN	UN	(+)	UN	UN	UN
Bockhorn	2004	50	F	Palpable nodule	0.8 (<4.6)	0.5	Malignant	MTC?	20	TT	Negative	(+)	(+)	(+)	UN
Sand	2006	73	F	Palpable nodule	5.3 (0.8–9.9)	NP	NP	NP	UN	TT+BRND	UN	(+)	(+)	UN	UN
Dora	2008	43	M	Palpable nodule	4 (<12)	0.78	Malignant	MTC?	17	TT	Negative	(+)	(+)	(+)	(+)
Wang	2008	68	M	Goiter	38 (<10)	56.7	MTC?	MTC	UN	TT+RND	Negative	(+)	(+)	(+)	(+)
Present study	2010	76	M	Incidentally found	10.5 (<10)	386	NP	MTC?		TT+ULND	Negative	NP	(+)	NP	NP

BLND, bilateral lymph node dissection; BRND, bilateral radical lymph node dissection; CEA, carcinoembryonic antigen; CT, ; FNAC, fine needle aspiration cytology; MTC, medullary thyroid carcinoma; ND, non-diagnostic; NP, no-performed; RND, radical node dissection; TT, total thyroidectomy; ULND, unilateral lymph node dissection; UN, unnoted.

as in some malignant diseases such as MTC. The literature contains a total of four MTC cases that were tested because of high CEA levels, as in our patient.[23]

CEA has been demonstrated to be a useful tumor marker in patients with MTC, and CEA levels are elevated in 50% of patients with MTC. A preoperative serum CEA level of >30 ng/mL is highly predictive of the inability to cure a patient with operative intervention. CEA levels of >100 ng/mL are highly associated with extensive lymph node involvement and distant metastasis.[13] CEA is an important marker for follow-up of postoperative relapses in patients with close to normal or mildly elevated calcitonin levels.

18F-fluoro-2-deoxyglucose-positron emission tomography (18F-FDG-PET) is taken up by cells with a high glucose metabolism or during the synthesis of catecholamines. ^{18}F-FDG-PET is used in the imaging of metastatic neuroendocrine tumors such as carcinoids and MTC. For MTC detection, ^{18}F-FDG-PET provides a higher sensitivity (76%–96%) and specificity (79%–83%) compared with morphologic imaging methods and can be used postoperatively to detect apparently occult MTC, especially in the cervical and mediastinal regions. However, ^{18}F-FDG-PET is generally not very useful in patients with mildly elevated calcitonin levels. Although the calcitonin level was slightly increased in the present case, successful outcomes were obtained with postoperative ^{18}F-FDG-PET.

Consequently, in cases found to have high CEA levels in blood tests conducted for any reason, neuroendocrine tumors, such as MTC, should be investigated after exclusion of gastrointestinal malignancies because an increased CEA level may be the first and only finding of MTC.

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