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Article *in* Thyroid · June 2005

Impact Factor: 4.49 · DOI: 10.1089/thy.2005.15.485 · Source: PubMed

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THYROID
Volume 15, Number 5, 2005

Case History

Disseminated Medullary Thyroid Carcinoma Despite Early Thyroid Surgery in the Multiple Endocrine Neoplasia-2A Syndrome

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A 5½-year-old boy, with a family history of multiple endocrine neoplasia (MEN)-2A syndrome, was evaluated for presence of MEN-2A and medullary thyroid carcinoma (MTC). DNA diagnostics confirmed MEN-2A. Basal (360 ng/L) and pentagastrin stimulated (430 ng/L) calcitonin (CT) levels were slightly elevated, plasma carcinoembryonic antigen (CEA) was normal. Within a year both tumor markers increased and total thyroidectomy was performed. Histologic examination did not show MTC. In the following years, both tumor markers increased progressively but despite the use of multiple imaging techniques no metastases were localized. After 6 years, biopsy of a palpable lymph node showed MTC. The boy was treated with total cervical, suprahyoidal, and mediastinal lymph node dissection, showing MTC in almost all nodes. Again, the tumor markers remained high. At this point in time, the disadvantages of further medical interventions were outweighed against the chance for cure and it was decided to shift the goal of treatment toward palliation rather than cure. At the last visit the boy was clinically well with persistent extremely high levels of plasma CEA and CT. In conclusion, when prophylactic thyroidectomy in the MEN-2A syndrome has failed, it may be best to withdraw from further interventions to prevent more damage.

Introduction

Carriers known to have the multiple endocrine neoplasia (MEN)-2A syndrome are at risk for developing medullary thyroid carcinoma (MTC) at a young age. Because radical surgery is the only curative option for MTC, prophylactic thyroidectomy is advised (1). For detection of recurrent disease, the tumor markers calcitonin (CT) and carcinoembryonic antigen (CEA) are useful. When these are elevated, evidence is provided that MTC is present. However, they do not provide information about the localization of MTC and visualization can be extremely difficult. It has been shown that patients can have substantial burdens of metastatic MTC without symptoms for many years (1) and it is still uncertain in these cases what the correct strategy should be (2). "Watchful waiting" is sometimes preferred, while others prefer prophylactic mantle irradiation or meticulous microdissection of the neck (2–4).

We report a case in which the many difficulties are illustrated that one can encounter after performing early thyroid surgery based on genetic testing.

Case Report

In 1993, a 5½-year-old, apparently healthy boy was examined because of a family history of the MEN-2A syndrome. The tumor markers CT and CEA were measured. The plasma concentration of CEA (2.8 μg/L) was normal, but both basal (360 ng/L) and pentagastrin stimulated (430 ng/L) CT levels were slightly elevated. Subsequent DNA diagnostics demonstrated the monoallelic mutation C634R in the *RET* proto-oncogene that confirms MEN-2A. Within a year both tumor markers for MTC increased and at age 7.0, total thyroidectomy without lymph node resection was performed. At histologic examination of the thyroid, no C-cell abnormality was found.

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Postoperatively, plasma thyroglobulin (radioimmunoassay) as marker for residue thyroid tissue was less than 10 pmol/L, however, both tumor markers increased progressively (Fig. 1). Multiple imaging techniques were used to localize metastases, without any result (Table 1). The thyroid tissue was reexamined, but again no C-cell hyperplasia or malignancy could be found. Six years later, a cervical lymph node became palpable. Biopsy showed MTC. On rerevision of the original thyroid tissue, multifocal C-cell hyperplasia was observed, laterally in the thyroid gland. Bilateral total cervical lymph node dissection demonstrated MTC in all lymph node sites. Nevertheless, both tumor markers further increased. This time, with ^{111}Indium-octreotide, a tiny spot in the mediastinum could be detected.

Subsequently, a total bilateral suprahyoidal and mediastinal lymph node dissection was performed, showing MTC in almost all nodes. Again though, the tumor markers remained high. While the boy never had any physical complaint of the MEN-2A, he had experienced serious discomfort because of the numerous invasive medical interventions, which were multiple surgical interventions, hypoparathyroidism as complication of surgery, multiple scars, subcutaneous calcifications caused by accidental leakage of intravenous calcium supplementation, multiple intravenous lines and biopsies for diagnostics, radiation burden, and last but not least, continuing emotional uncertainties. As a consequence and in view of the dissemination of the disease, it was decided that the goal of treatment should be shifted toward palliation rather than cure. The boy and his parents agreed that no more additional invasive investigations would be performed. Of course, it was guaranteed that in addition to thyroid hormone and calcium supplementation, maximum medical care would always be provided if the boy were to develop any symptoms or complaints from the disease. At the last visit the boy was 16.5 years old and clinically well with still extremely high levels of plasma CEA and CT (676.0 μg/L and 4500 ng/L, respectively).

Discussion

For patients with the MEN-2A syndrome, the risk to develop MTC in 90%–100% (1,5). Because MTC is not sensitive to chemotherapy or radiotherapy, all C-cells have to be removed before they metastasize by performing total thyroidectomy (1). Simultaneous central lymph node removal is recommended by some, but no consensus has been achieved (6). During the last decade the possibilities for genetic testing have been brought to perfection, and theoretically prevention of MTC is possible at any age. The ideas for preventive action have changed gradually in time, because of increasing knowledge about risk in relation to age. At the time that DNA diagnostics in our patient had proven the MEN-2A syndrome, it was considered safe to postpone thyroidectomy until testing with pentagastrin demonstrated C-cell hyperplasia. Currently, prophylactic thyroidectomy is recommended before the age of 5 years (1), although MTC has been diagnosed already in a 1-year old patient with MEN-2A (6). From the pediatric point of view, there is no technical age limitation to thyroidectomy, and thyroid hormone replacement has favorable outcome as evidenced by early treatment of infants with congenital hypothyroidism caused by thyroid agenesis. Despite this point of view, the discrepancies between genomics and clinics will persist because of physical limitations of the individual patient and (parental) emotions that have to be taken into consideration before deciding on thyroidectomy. For detection of recurrent MTC, plasma levels of CT and CEA are reliable determinants. The secretion of CT can be remarkably increased by calcium or pentagastrin infusion. Elevated CT and CEA concentrations do not, however, provide information about the localization of the metastases, and visualization can be extremely difficult. ^{131}I-MIBG, ^{111}In-octreotide, ^{99m}Tc-anti-CEA, ^{99m}Tc-EDDA/HYNIC-TOC, or positron emission tomography (PET) can be used, all with low sensitivity. When MTC is localized, external radiotherapy may improve tumor control in residual disease (7). If the tumor cells take up the compound, targeted radionuclide therapy may also be use-

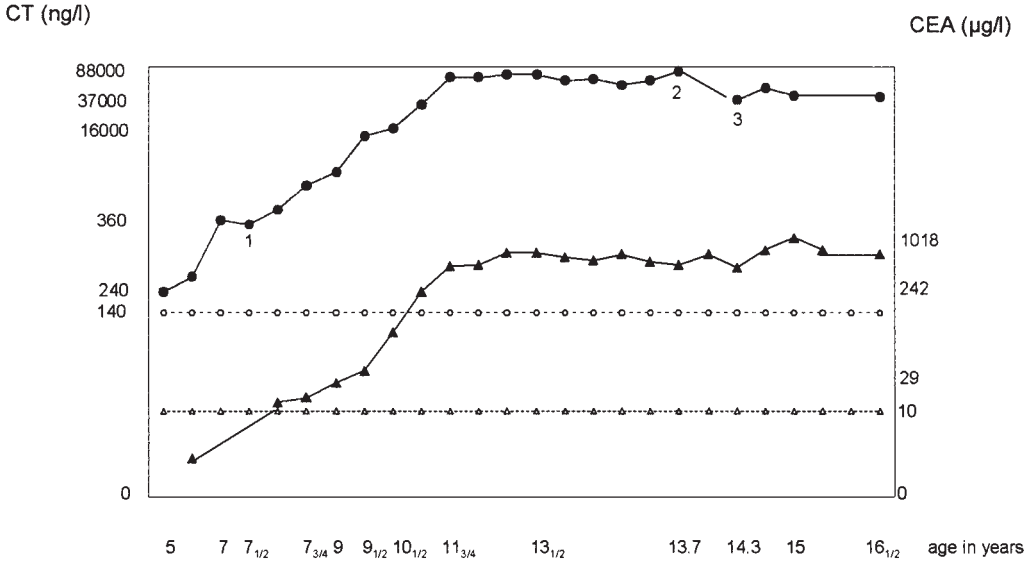

FIG. 1. Time course of the (logarithmic) plasma concentrations of carcinoembryonic antigen (CEA) and calcitonin (CT) after thyroidectomy ● = calcitonin (CT), ○ = upper normal limit for CT, ▲ = carcinoembryonic antigen (CEA), △ = upper normal limit for CEA. [1]Age 7, total thyroidectomy; [2]age 13.7 years, radical bilateral cervical lymph node dissection; [3]age 14.3 years, sternotomy with supra-hyoidial and mediastinal lymph node dissection.

Table 1. Investigations Performed to Detect Metastases of MTC

Age (years)	*Imaging technique*	*Result*
7.7	Ultrasound neck	Small lymph node left side, ventral of neck vasculature
7.8	Ultrasound abdomen	N.a.
	Ultrasound neck	N.a.
8	^{111}-In Octreoscan (whole body and SPECT)	N.a.
8.5	^{123}I-MIBG-scan (117 MBq)	Possible increased uptake in the abdomen, just below/under diaphragm, can be an artifact
	Pentavalent DMSA-scan	N.a.
8.6	Ultrasound abdomen	N.a.
9	MRI abdomen	N.a.
	X-thorax	N.a.
9.1	MRI thorax	N.a.
9.5	Ultrasound neck	Lymph node right neck 7–3 mm, left side 5–3 mm, presumably reactive lymph nodes
	X-thorax	N.a.
9.7	CT-thorax and neck	N.a.
	^{99m}Tc-antiCEA scan (556 MBq)	Very subtle spot high anterior in the neck (left side), but no pathological uptake
10.6	X-thorax	N.a.
11.7	X-thorax	N.a.
	Ultrasound neck	Multiple small lymph nodes right and left side, seem to be reactive lymph nodes
12.3	^{123}I-MIBG-scan, whole body and SPECT (158 MBq)	Ventral, caudally in the right liver lobe, small area of increased uptake, presumably an artifact
	^{111}In-Octreoscan (152 mBq) whole-body and SPECT	N.a.
12.5	Ultrasound abdomen	Medullary sponge kidneys, no pathological lymph nodes
	Ultrasound neck	No thyroid rest, multiple lymph nodes right and left, can be normal at this age
13.7	PET-scan (0.29 BGq ^{18}F-FDG)	N.a.
	Ultrasound neck	Multiple lymph nodes both sides of the neck, puncture performed in one.
14	^{111}In-Octreotide scan (224 MBq)	Positive pathologic uptake halfway the mediastinum, could be thymus tissue.
14.1	^{99m}Tc-anti-CEA scan (644 MBq)	N.a.
15.7	Ultrasound abdomen	N.a.
	X-thorax	N.a.

N.a., no abnormalities; MIBG, meta-iodobenzylguanidine; MBq, megabequerel; FDG, fluorodeoxyglucose; In, Indium; SPECT, single-photon emission tomography; MRI, magnetic resonance imaging; CT, computed tomography.

ful for palliation. For a minority of patients, with rapidly progressive metastatic tumor, palliative chemotherapy may be recommended. As the gain-of-function mutation in the *RET*-proto-oncogene leads to an increased activity of tyrosine kinase and cell growth, the use of a protein-tyrosine kinase inhibitor has been studied (8). Trials using genetic cytokine immunotherapy give promising results, but dose dependency and systemic toxicity are a problem in studies concerning both animal and humans. For this reason, effective gene therapy using recombinant adenovirus has been studied. In animal and *in vitro* studies, this has shown to be effective with less toxicity (9). In humans, however, such studies have not been performed.

Patients can have substantial burdens of unlocalized, metastatic MTC for many years, without symptoms (1) and there is no consensus on the best strategy for these cases. In our patient, within a year after thyroidectomy, unstimulated levels of CT and CEA rose to extremely high levels, indicating

early metastatic MTC. Because the original pathologic evaluation did not show any malignant cells, time was taken to locate the tumor or metastases, without success. Because surgery is the only curative option, the boy was treated aggressively with multiple surgical interventions but none turned out to be curative.

In conclusion, this case illustrates the many difficulties one can encounter when confronted with a DNA diagnosis of a malignant syndrome or with elevated tumor markers in a child without clinical symptoms or without localized tumor. Difficulties include when and to what extent to perform surgery, difficulties regarding the histologic examination of the thyroid tissue, difficulties in localizing metastases, and what to decide when prophylaxis has failed. In such a situation, it is important to decide, when to aim for palliation to prevent additional physical damage and emotional burden to the patient.

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