Medullary Thyroid Carcinoma

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Chapter 2

Medullary thyroid cancer, a tumour with many appearances

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Abstract

Medullary thyroid cancer (MTC) has a variable clinical presentation. We present 3 patients with this endocrine tumour. The first patient, a 41-year-old woman complaining of diarrhoea, a painful abdomen, weight loss and sensibility disorders in both legs, had metastases of MTC in the spine, with little progression during 2 years of follow-up. The second patient, a 64-year-old woman suffering from a painful nodule in the neck and a painful shoulder, was diagnosed with MTC and liver, lung and bone metastases. She died after 14 months due to progressive disease. The third patient, an 81-year-old woman with hyperparathyroidism, was coincidentally diagnosed with MTC after goitre surgery at the age of 67. When she was evaluated for rising calcitonin levels, a pheochromocytoma was found. RET mutation analysis confirmed a MEN2A syndrome. Current diagnostic procedures of MTC may include positron emission tomography with 18F-deoxyglucose (^{18}F-FDG PET) and 18F-diphenylalanine (^{18}F-DOPA PET). MTC is usually treated surgically. Tyrosine kinase inhibitors also appear to offer potential new therapeutic possibilities.

Introduction

Medullary thyroid carcinoma (MTC) is a rare endocrine tumour which originates from the calcitonin producing C-cells in the thyroid. The serum level of calcitonin has therefore a great diagnostic value as tumour marker. Also the serum level of carcinoembryonic antigen (CEA) is often elevated, but is less specific for MTC. In the Netherlands, 20-30 MTC patients are diagnosed yearly. MTC can occur sporadically (75% of cases) or familiarly as part of the multiple endocrine neoplasia type 2 syndrome (MEN2). Of this syndrome, caused by a mutation in the 'REarranged during Transfection (*RET*)' gene, a MEN2A and MEN2B variant are known (Table 1).[1] Here we illustrate the broad spectrum of presentation and the clinical course of MTC with 3 patients. Furthermore the current diagnostic modalities and treatment options are discussed.

Patient A, a 41 year old woman, presented with a multinodular goitre. Repeated fine needle aspiration cytology (FNAC) of the thyroid did not reveal malignancy. Four years later she presented with diarrhoea, a painful lower abdomen and a weight loss of 13 kg. Additional investigation, which included gastroduodenoscopy, colonoscopy, abdominal and transvaginal ultrasound (US), did not lead to a diagnosis. She then developed an abnormal walking pattern with sensibility dysfunction of both legs. Magnetic resonance imaging (MRI) showed a tumour in the sixth thoracic vertebrae with compression of the myelum. Surgical debulking took place and the pathologist diagnosed a metastasis of a MTC. The calcitonin and CEA were highly elevated (respectively 143,150 ng/l (ref 0.3-12 ng/l) and 1400 ug/l (ref 0.5-5 ug/l)). The serum calcium was normal and there were no hints of pheochromocytoma. Additional *RET*-mutation analysis did not show a mutation. Further investigations for staging with fluor-18-deoxyglucose (^{18}F-FDG) positron emission tomography (PET) and fluor 18-dihydroxyphenylalanine (^{18}F-DOPA) PET showed the primary process in the thyroid with extensive bone metastasis (Figure 1). A total thyreoidectomy with lymph node dissection of the central compartment was performed. In this procedure all lymph nodes and fat tissue between both carotids was removed, from the os hyoideum cranially to the v. brachiocheplica caudally. After surgery a single dose with 150 mCurie I131 MIBG was given for persisting diarrhoea, with a subjectively good response. At this moment four years after MIBG therapy there is slowly progressive disease, which is too slow for inclusion in a clinical trial with a tyrosine kinase inhibitor.

Table 1 Clinical characteristics of patients with familial medullary thyroid carcinoma, multiple endocrine neoplasia (MEN) 2A and MEN2B.

Clinical characteristic	Prevalence (%)		
	Familial MTC*	MEN2A	MEN2B
Medullary thyroid carcinoma	100	100	100
C-cell hyperplasia	100	100	100
Pheochromocytoma	0	10-60	50
Hyperparathyroidism	0	10-25	0
Neurofibromatosis	0	0	60-90
Marfanoid habitus	0	0	100

* Families are described in which only MTC occurs without other endocrine neoplasia's.

Patient B, a 64–year old female presented with a painful nodule in the neck and a painful right shoulder in another hospital. FNAC of the nodule showed a MTC. Ultrasound of the liver, CT-imaging of the abdomen and bone scintigraphy showed metastasis in the liver and skeleton, upon which referral to our centre was made. Additional imaging with ^{18}F-FDG PET showed besides liver metastasis also neck and lung metastasis. Calcitonin serum levels were strongly elevated (650 ng/l); CEA was not determined and no biochemical clues existed for a pheochromocytoma or hyperparathyroidism. *RET*-mutation analysis was not performed because the patient was above 50 years and there was no clinical suspicion of a MEN2 syndrome. For local control of the primary tumour, a total thyroidectomy with a central and lateral lymph node dissection was performed. External radiotherapy was given postoperatively in the neck and mediastinum (70 Gy in 35 fractions). There was, however, biochemical progression and progression on ^{18}F-FDG and ^{18}F-DOPA PET, especially of the bone metastasis, for which palliative radiotherapy was given. Because of her poor clinical condition, no systemic therapy was started. The patient deceased fourteen months after initial presentation.

Patient C, an 81 year old woman, had at the age of 67 undergone in another hospital a subtotal thyroidectomy and parathyroidectomy for a primary hyperparathyroidism and goitre. Histopathological investigation revealed a hyperplasia of the parathyroids and a coincidental MTC; no information on tumour size was available. An additional total thyroidectomy without lymph node dissection was performed.

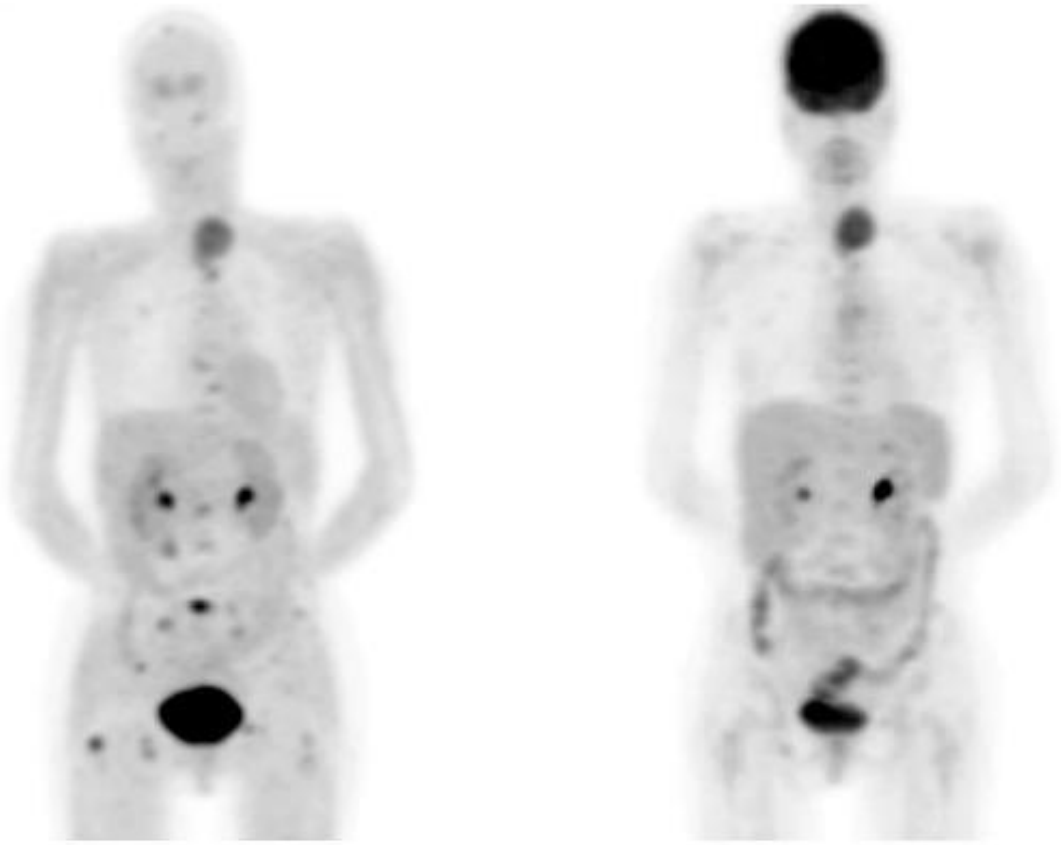

Figure 1 Positron emission tomography with ^{18}F-DOPA PET (left) and ^{18}F-FDG PET (right) of patient A. The ^{18}F-DOPA PET shows clear uptake in the primary tumour in the neck. Extensive bone metastasis in the skull, spine, skull and both femora is present. There is physiological uptake of ^{18}F-DOPA in the putamen, the caudate nucleus, kidneys and bladder. The ^{18}F-FDG PET shows also clear uptake in the primary tumour and focal uptake in the pelvis and right femur. There is faint uptake in the area of the 6th thoracic vertebra, because of surgical debulking 6 weeks before the scan. There is physiological uptake in the brain, kidneys, bladder and colon.

The patient was referred to our centre for further analysis of rising serum calcitonin levels; the CEA concentration was not elevated. For a period of four years she had paroxysmal occurring heat sensations without other symptoms. Blood pressure was 170/74 mm Hg, and further physical examinations revealed no abnormalities. Biochemical investigation showed, besides a raised serum calcitonin concentration, also increased metanephrines in plasma and urine, suggestive of a pheochromocytoma. Imaging revealed enlarged lymph nodes in the neck and an adrenal tumour on the left.

A laparoscopic adrenalectomy was performed with removal of a pheochromocytoma. DNA analysis was performed because of the clinical presentation, despite the high age. The patient was carrier of a Cys618Phe mutation of the *RET*-gene, a single base substitution in codon 618, in exon 10, resulting in the amino acid substitution of cysteine by phenylalanine. This

confirmed the clinical diagnosis MEN2A. Because of the high age of the patient and the lack of clinical symptoms a 'wait and see' policy for the MTC was adopted. In the family of the patient genetic analysis was performed over four generations. Of the 40 family members investigated, 19 carried the Cys618Phe mutation.

These patients show the varied clinical course of MTC. The presentation of patients A and B is characteristic for a sporadic MTC, in which at the time of diagnosis extensive metastasis is already present. It's likely that a MTC was already present when patient A presented with goitre. This shows that patients with metastasized disease can survive for many years. The progressive and fatal nature of MTC is illustrated by the clinical course of patient B. The clinical course of patient C shows the sometimes mild course of MTC with a *RET*-mutation. Most *RET*-mutations result in an aggressive biological behaviour, but in some patients the clinical course is more favourable. The mutation of our patient had great implications for her family, because carriers of the mutation are candidates for prophylactic thyroidectomy, with or without central compartment dissection and lifelong follow-up for possible occurrence of a pheochromocytoma and primary hyperparathyroidism.

Clinical presentation

Patients with MTC most often present with a palpable tumour in the neck. More than 50% of patients already have lymph node metastases at the time of diagnosis and 15% have distant metastasis.[2] Patient A presented with diarrhoea, a symptom that can occur due to hypersecretion of calcitonin.[1] In patients with long term unexplained diarrhoea, MTC can be considered in differential diagnosis. Retrospectively, patient C presented with at that time unrecognised manifestations of MEN2A. Failure to recognise this syndrome can lead to inadequate diagnosis and therapy. The patient did have a pheochromocytoma and had therefore an increased risk of a potentially fatal hypertensive crisis.[3]

Diagnosis

According to current guidelines, an ultrasound guided FNAC in a solitary thyroid nodule is preferred.[4] In 63%-89% of MTC patients this gives the correct diagnosis, and 91%-100% of MTC patients are operated based on FNAC results.[1] When FNAC is inconclusive, determination of serum calcitonin and CEA can be helpful. Calcitonin is a sensitive tumour marker (sensitivity 98%), but there is still discussion about the cost-effectiveness because

thyroid nodules are common, MTC is relatively rare and false-positive findings occur frequently.[1,5]

Morphological imaging with CT or MRI can be used for staging. Before starting treatment it's important to know if and where MTC metastases are present. To determine this, functional imaging with ^{18}F-FDG PET and ^{18}F-DOPA PET can be used, because morphological imaging is less sensitive. Fluor-18-DOPA is a relatively new tracer for imaging of neuroendocrine tumours. DOPA is a precursor in the catecholamine synthesis, which specifically occurs in many of these tumours. ^{18}F-DOPA PET has the highest sensitivity while ^{18}F-FDG PET is more often positive in patients with a progressive tumour.[6]

Because of the risk of MEN2, which inherits autosomal dominantly, every patient with MTC under the age of 50 is a candidate for genetic screening. Pre-operative determination of serum calcium and metanephrines is indicated in all patients with MTC to rule out hyperparathyroidism or pheochromocytoma. Manifestations of a MEN2 can then be diagnosed and treated at an early stage.

When a *RET*-mutation is established in a patient, genetic screening of family members is necessary to offer carriers – including children – a prophylactic thyroidectomy.[7] The age of children undergoing such a procedure varies between one and ten year and depends on the mutation. Early recognition and adequate treatment of MTC in this way can prevent severe morbidity and mortality.

Treatment

Primary tumour

The treatment of MTC is primary surgical and consists of a total thyroidectomy and possible additional lymph node dissection.[8] The extent of the lymph node dissection depends on the expansion of the primary tumour and the presence of lymph node or distant metastasis.

Recurrence

The treatment of locoregional recurrent disease is also surgical. If there is curative intent an extensive systematic central and lateral lymph node dissection is performed. If there are distant metastases, the procedure is less extensive and more focussed on locoregional control, and locoregional radiotherapy can be given.[9] Iodine-131 can be given if there is proven uptake of this tracer.[1] Another option for therapy is radioactive labelled octreotide.[10] However both

therapies have modest results. Currently no effective systemic treatment is available and only treatment in a clinical trial is advised.[2]

Follow-up

Measurement of serum calcitonin and CEA levels are important in the follow-up of patients with MTC. A raised or raising tumour marker indicates local recurrent disease or metastasis. Additional morphological and functional imaging can determine localisation, after which possible treatment can be given.

Prognosis

The 10 year survival rate of MTC is around 75%.[1] The most important prognostic factors are the extent of the primary tumour at the time of diagnosis and the presence of lymph node or distant metastasis. Despite the wide spectrum of available diagnostic modalities, MTC is often diagnosed in a late stadium and survival has barely increased during the last decades.[1]

New therapeutic options

A large proportion of sporadic MTC patients has persistent disease activity with locoregional recurrent disease and distant metastasis. Tyrosine kinase inhibitors might give these patients new perspectives. These drugs target tyrosine kinase mediated signal transduction in malignant C-cells. The RET receptor is a tyrosine kinase which is active in a large proportion of the MTC patients, causing uninhibited proliferation of C-cells.[1,7] The RET-receptor might therefore be a good target for this antiproliferative therapy.

Multikinase inhibitors

Multikinase inhibitors like vandetanib and XL-184, which not only target the RET-receptor but also other receptors like the vascular endothelial growth receptor (VEGFR) and the mesenchymal-epithelial-transitionfactor (MET)-receptor are promising, with reported tumour responses in 20%-33% of patients and stable disease in 25%-53%.[11,12] However, in a proportion of patients no effects have been seen. Therefore development of new drugs or combination therapy is necessary.[1,7]

Conclusion

MTC is a rare tumour with different presentations. Because an apparent sporadic MTC can be the first manifestation of a MEN2 syndrome, pheochromocytoma and hyperparathyroidism have to be ruled out preoperatively through biochemical analysis. Furthermore RET-mutation analysis is recommended, at least in patients under the age of 50 and in patients with a clinical suspicion. In this case, family members can also be screened and prophylacticly treated if a mutation is found. MTC patients are preferably treated in a multidisciplinary centre with extensive experience in thyroid surgery, endocrinology, genetics and nuclear medicine.

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