Diagnosis of medullary thyroid cancer

Stefania Marchisotta and Furio Pacini*

Address: Dipartimento di Medicina Interna, Scienze Endocrino-Metaboliche e Biochimica, Sezione di Endocrinologia e Metabolismo, Università di Siena, Viale Bracci, 53100 Siena, Italy

*Corresponding author: Furio Pacini (pacini8@unisi.it)

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Abstract

Medullary thyroid cancer (MTC) accounts for 5–10% of all thyroid cancers. The majority of medullary thyroid cancers are sporadic, but 25% of cases are inherited as a result of germline mutations in the *RET* proto-oncogene. In sporadic cases MTC presents as a thyroid nodule discovered at palpation or at thyroid ultrasonography, and is indistinguishable from thyroid nodules of different histology. Since effective treatment of MTC is only possible when the tumour is limited to the thyroid gland, early discovery has a decisive impact on how radical initial surgical treatment needs to be. Recent data suggest that in sporadic cases, early discovery of thyroid nodular disease is possible when screening serum calcitonin measurement, while screening for germline *RET* proto-oncogene mutations is fundamental in first degree relatives of patients with hereditary MTC.

Introduction and context

Medullary thyroid cancer (MTC) is a malignant tumour originating from the calcitonin producing parafollicular (C) cells of the thyroid. Among well-differentiated thyroid carcinomas, it is the most aggressive, with survival rates of 40–50% at 10 years. Early diagnosis and radical surgical treatment are key to improving morbidity and mortality amongst patients with MTCs [1]. Fine needle aspiration cytology (FNAC) is a very sensitive and specific procedure for the diagnosis of malignant thyroid nodules, but cytological typing of MTC may be difficult with routine staining. Serum calcitonin (CT) measurement in patients with thyroid nodules is the most specific and sensitive marker of MTC, having even better accuracy than FNAC in diagnosing unsuspected MTC [2–3]. An elevated level of serum CT, confirmed by an exaggerated response to pentagastrin stimulation, is almost invariably associated with MTC.

Hereditary MTC accounts for 25% of cases and is transmitted with an autosomal dominant pattern caused by germline mutation of the *RET* proto-oncogene, coding for a transmembrane tyrosine kinase (TK) receptor mapped to chromosome 10q11.2 [4–6]. The

hereditary form of MTC may be associated with other endocrine neoplasias such as pheochromocytoma and parathyroid adenomas (multiple endocrine neoplasia type 2A, or MEN 2A), or pheochromocytoma and mucosal neurinomas (multiple endocrine neoplasia type 2B, or MEN 2B). Alternatively, the hereditary form may be the only manifestation of the disease (familial MTC, or FMTC) [7].

In 1987, the MEN2A gene was assigned by linkage analysis to the pericentromeric region of chromosome 10 [8,9]. In 1993, MEN 2A and FMTC were shown to be associated with mutations in exon 10 or 11 of the *RET* proto-oncogene, and specific *RET* mutations were detected in affected families [4,5]. Subsequently, *RET* proto-oncogene mutation was also found to be involved in MEN 2B [6].

The proto-oncogene *RET* comprises 21 exons and encodes a receptor TK that has a large extracellular domain, a single transmembrane region, and two cytoplasmic TK domains. Approximately 95% of MEN2A families have mutations involving exons 10 (codons 609, 611, 618, and 620) and 11 (codon 634) of

the *RET* proto-oncogene, which encode the cysteine-rich domain of the RET receptor. *RET* mutations that affect the intracellular TK domain, however, are rare. Mutations that involve the cysteine-rich extracellular domain of the RET receptor are thought to cause disease through constitutive dimerization and activation of the receptor.

The FMTC phenotype is associated with mutations involving both the extracellular cysteine-rich and intracellular TK domains of the RET receptor. These mutations are located in exons 10 (codons 618 and 620), 11 (codons 630, 631, and 634), 13 (codons 768, 790, and 791), 14 (codons 804 and 844), and 15 (codon 891). 95% of cases of MEN 2B are associated with a point mutation in the methionine residue in exon 16 (codon 918) in the intracellular TK domain of RET; this is thought to induce tumour formation by altering the substrate specificity of the kinase domain, thereby activating growth-stimulating pathways [10].

Recent advances

Recently, the European Thyroid Association (ETA) has included routine measurement of serum CT in the diagnostic evaluation of thyroid nodules. In contrast with ETA [11] recommendations, the American Thyroid Association (ATA) guidelines are neither in favor nor against routine measurement of serum CT in patients with thyroid nodules [12], although a recent American study [13] demonstrated that it has a cost effectiveness comparable to thyroid stimulating hormone (TSH) measurement, mammography and colonoscopy screening. This study is the first effort to measure the cost effectiveness of CT screening in the USA. Evidence such as this is essential and should prompt physicians to screen thyroid nodules by serum CT measurement in their clinic, and should contribute to the improvement of practice guidelines.

Another recent study suggests extending the screening for the *RET* proto-oncogene to every patient with MTC. Since 1993, screening for the germline *RET* mutation has been introduced to define the hereditary nature of an MTC tumour in the first affected family member that seeks medical attention (the proband) and, where positive, to search for additional family members carrying the mutation (50% risk of carrying the mutation). If the screening is performed early in life, it can identify the member at risk even before development of the disease, or at least at an earlier stage. The practical consequence is the possibility of performing prophylactic total thyroidectomy or beginning early treatment of the limited disease. *RET* genetic screening is also indicated in patients apparently presenting with the sporadic form.

Elisei *et al.* [14] demonstrated that germline *RET* mutations are present in 7.3% of patients erroneously diagnosed with sporadic MTC. Reclassifying this form as hereditary has a great clinical impact on the discovery of new MTC families.

Although the entire spectrum of genetic alterations causing sporadic MTC has not yet been defined, nearly 50% of sporadic MTCs harbour a somatic point mutation of the *RET* proto-oncogene. It is reported that patients with sporadic MTCs carrying a somatic *RET* mutation have a worse outcome compared with patients who have *RET* negative tumours [15–17]. The identification of the *RET* mutation in the DNA extracted from FNAC could help in planning a more aggressive surgical strategy in *RET*-positive cases, hopefully improving the long-term survival.

Implications for clinical practice

In conclusion, early diagnosis is mandatory for effective treatment of MTC. In sporadic cases this can be achieved through routine screening of thyroid nodules by serum CT and in familial cases by genetic *RET* screening of family members of a proband with hereditary MTC. In addition, the screening of tumour DNA from all MTC patients for *RET* somatic mutations may not only help to distinguish sporadic MTCs from familial forms (with important clinical and predictive consequences), but will also be useful in the prediction of clinical outcomes and designing therapy for patients with certain sporadic tumours carrying a *RET* somatic mutation [15].

Abbreviations

CT, calcitonin; ETA, European Thyroid Association; FMTC, familial medullary thyroid cancer; FNAC, fine needle aspiration cytology; MEN 2A, multiple endocrine neoplasia type 2A; MEN 2B, multiple endocrine neoplasia type 2B; MTC, medullary thyroid cancer; TK, tyrosine kinase.

Competing interests

The authors declare that they have no competing interests.

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