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Medullary Carcinoma of the Thyroid Gland

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Abstract. Medullary thyroid carcinoma (MTC) is an uncommon thyroid tumor that has attracted a great deal of interest because of its frequent presentation as a familial tumor and its primary involvement in the type II multiple endocrine neoplasia (MEN) syndromes MEN-IIA and MEN-IIB and familial medullary thyroid carcinoma (FMTC). The MTC tumor cells secrete the polypeptide hormone calcitonin, which serves as an excellent tumor marker, useful for defining the presence of disease, preoperatively or following thyroidectomy. The discovery that mutations in the *RET* proto-oncogene are associated with MEN-II syndromes was highly significant in that it demonstrated a clear correlation between genotype and phenotype; and most importantly it provided a mechanism whereby family members at risk could be identified by direct DNA analysis. Virtually all patients with MEN-IIA, MEN-IIB, and FMTC develop MTC; therefore there is a clear rationale for performing thyroidectomy as soon as a *RET* mutation has been identified. Because MTC appears to be much more aggressive in patients with MEN-IIB, thyroidectomy is performed during the first year of life in this setting, whereas in patients with MEN-IIA, where the tumor appears to be more indolent, the procedure can be safety delayed until age 5 years. Reoperative neck exploration in patients with evidence of persistent or recurrent MTC has been effective in a significant number of patients, although the success of the operation requires careful patient selection and preoperative assessment. MTC, as expressed in the MEN-II syndromes, is an excellent model to evaluate the usefulness of interventional therapy in patients demonstrated to have a genetic predisposition for cancer.

Medullary carcinoma of the thyroid gland (MTC) is an uncommon tumor, accounting for 5% to 10% of all thyroid malignancies. Surprisingly, the cancer was not recognized as a specific pathologic entity until 1959 when Hazzard et al. reviewed 600 cases of thyroid carcinoma at the Cleveland Clinic over a 31-year period and identified 21 tumors with unique histologic features, which they termed medullary thyroid carcinoma [1]. Here we review the specific characteristics of MTC, including its histologic and biochemical features, its clinical presentation (including the laboratory and molecular methods of establishing the diagnosis), and its treatment.

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Histology and Biochemistry

Medullary thyroid carcinoma develops in C cells, which are located in the superior portions of the thyroid lobes. These cells derive from the neural crest and are unrelated to the thyroid follicular cells. In birds and fishes, C cells are congregated in a separate structure called the ultimobranchial body. Aliepoulios and Rose demonstrated the relevance of C cell distribution in the thyroid lobes to the multicentric development of MTC [2]. Macroscopically, MTC has a solid appearance, and the cut surface is white and gritty. Histologically, the tumors have a spindle cell appearance; and on special staining they have properties characteristic of amyloid. However, the material is not amyloid but a prohormone for calcitonin, a polypeptide hormone secreted by the C cells.

C-cell hyperplasia (CCH) is a histologic abnormality that precedes the development of MTC. This histologic entity was first described by Wolfe and associates and represents multicentric clusters of C cells in the thyroid parenchyma [3]. In most patients the MTC grows slowly and with time metastasizes to regional lymph nodes. The most common sites of distant metastases are liver, lung, bone, and brain.

The C cells have great biosynthetic activity and secrete several hormones and biogenic amines, including calcitonin (CT), ACTH, histaminase, carcinoembroyogenic antigen, and vasoactive peptides. Of these the most important clinically is CT, which serves as an excellent tumor marker for MTC [4]. Intravenously administered calcium and pentagastrin are important CT secretagogues, and the plasma level of CT is an accurate indicator of the C-cell mass [4, 5]. Often in a patient at genetic risk for developing MTC the physical and radiographic examinations are normal and an elevated plasma CT level is the only evidence of a C-cell disorder. Also, measuring stimulated plasma CT levels following thyroidectomy is a valuable means of determining whether patients are cured of MTC or have persistent or recurrent disease. Since the development of direct DNA testing for the familial forms of MTC, the role of preoperative plasma CT measurement is unclear, although determination of plasma CT levels following thyroidectomy remains of great clinical importance.

Table 1. Clinical presentation of medullary thyroid carcinoma.

Type	Thyroid distribution	Familial pattern	Associated abnormalities	Biologic virulence
Sporadic	Unilateral	No	None	3+
MEN-IIA	Bilateral	Yes	Pheochromocytoma Hyperparathyroidism	2+
MEN-IIB	Bilateral	Yes/no	Pheochromocytoma Mucosal neuroma Ganglioneuroma Characteristic phenotype	4+
FMTC	Bilateral	Yes	None	1+

MEN-IIA, MEN-IIB: type II multiple endocrine neoplasia syndromes; FMTC: familial medullary thyroid carcinoma.

Clinical Presentation

Medullary thyroid carcinoma occurs sporadically or in a familial pattern as an integral part of MEN-IIA, MEN-IIB, or FMTC. MEN-IIA is characterized by the concurrence of MTC, pheochromocytomas, and parathyroid hyperplasia [6]. Virtually all patients with MEN-IIA have MTC, but only 50% have pheochromocytomas and 30% have hyperparathyroidism. Patients with MEN-IIB have MTC and pheochromocytomas but do not develop hyperparathyroidism. These patients also have marked neural hypertrophy characterized by mucosal neuromas and ganglioneuromas and a characteristic phenotype [7]. Kindreds with FMTC have only medullary thyroid cancer with none of the extrathyroidal endocrinopathies or clinical features associated with MEN-IIA or MEN-IIB [8]. Each of the familial forms of MTC is inherited in an autosomal dominant pattern with nearly complete penetrance but variable expressivity. Also, depending on the clinical presentation of MTC the tumors progress rapidly (MEN-IIB) or slowly (FMTC). The characteristic modes of presentation of MTC are compared in Table 1.

Physical Examination

A patient with the sporadic form of MTC almost always presents with a cervical neck mass and on examination has a thyroid nodule with or without enlarged lymph nodes in the lateral neck. In such patients it is important to exclude the presence of metastatic disease in the lungs and liver by conventional radiographic techniques. Patients with MEN-IIA, MEN-IIB, or FMTC may also present with a neck mass. Additionally, patients with MEN-IIA or MEN-IIB may complain of symptoms characteristic of a pheochromocytoma. When the diagnosis of MTC is established in a patient, regardless of the clinical setting it is imperative to exclude the presence of a pheochromocytoma prior to operating on the thyroid tumor.

In patients with sporadic MTC the thyroid neoplasms occur as solitary nodules and occupy only one thyroid lobe. However, in patients with MEN-IIA, MEN-IIB, and FMTC the MTC is bilateral, often multicentric, and almost always associated with C-cell hyperplasia. The frequency with which C-cell hyperplasia occurs in the thyroid glands of normal persons and in patients with sporadic MTC is controversial. Therefore, the presence of bilateral MTC in a patient who has no family history of this disease should alert the clinician to the presence of a MEN-II syndrome.

Biochemical Examination

The cornerstone to the diagnosis of MTC is the measurement of plasma CT levels following intravenous administration of calcium and pentagastrin. It is important to use both of these provocative agents as previously described, as the combined infusion produces higher plasma CT levels than does infusion of either agent alone [5]. The plasma CT level can be determined by commercial laboratories from which normal reference values are obtainable. The presence of a pheochromocytoma can be detected by measuring 24-hour urinary excretion rates of catecholamines and metabolites. The diagnosis of hyperparathyroidism can be established by documenting elevated serum levels of calcium and parathyroid hormone.

In members of kindreds with MEN-IIA, MEN-IIB, or FMTC who are at direct risk for developing MTC, the measurement of plasma CT levels following provocative testing often establishes the presence of MTC or C-cell hyperplasia even though there is no clinical evidence of disease.

Molecular Testing

In 1993 and 1994 novel missense mutations in the *RET* protooncogene were detected in patients with MEN-IIA, MEN-IIB, and FMTC [9–12]. The structure of the RET protein includes an extracellular ligand-binding domain with homology to the cadherin family of cell adhesion molecules, a transmembrane domain, and an intracellular tyrosine kinase catalytic portion split into two separate domains. Since glial-derived neurotrophic factor (GDNF) was first described as a ligand for RET, two additional ligands, persephin and neurturin, have been described [13–15]. Embryologic studies in mice suggest a role for RET in the derivation and migration of the neural crest cells and in the development of the genitourinary and gastrointestinal systems [16, 17]. Mice homozygous for a targeted mutation in *RET* have renal agenesis, failure of the development of enteric neurons, and early death [18]. In keeping with findings in the mouse model, loss of function has been shown to occur in a subset of patients with familial Hirschsprung's disease [19].

In more than 95% of families with MEN-IIA the missense mutations involve one of five codons in exons 10 and 11, each of which is a highly conserved cysteine residue in the extracellular portion of the receptor immediately adjacent to the cellular membrane. It has also been found that in patients with MEN-IIA there is a clear correlation between the specific genetic mutation and

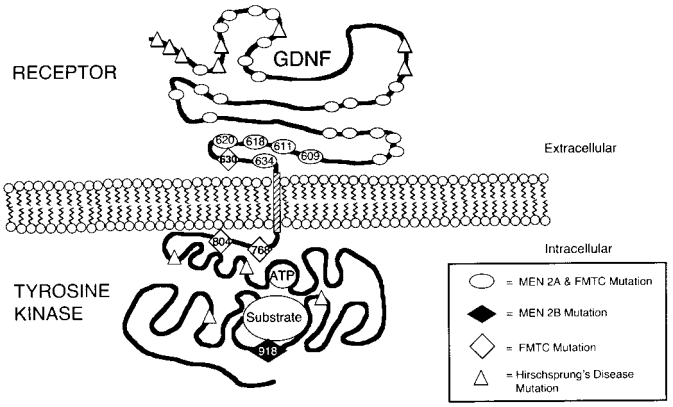

Fig. 1. RET protein receptor tyrosine kinase. MEN-IIA, familial medullary thyroid cancer (FMTC), MEN-IIB, and Hirschsprung's mutations in the *RET* proto-oncogene. The ligand is shown binding to the extracellular receptor. The adenosine triphosphate (ATP) molecule is bound at the ATP binding site near the substrate for the tyrosine kinase catalytic domain. The 28 cysteine residues in the extracellular receptor domain are depicted by the ellipses. The cysteine residues at codons 609, 611, 618, 620, and 634, associated with MEN-IIA and FMTC, are at the juxtamembrane region of the receptor. Mutations at codons 768 and 804 are associated with FMTC. The mutation Met_{918} to Thr (ATG to ACG) associated with MEN-IIB (indicated by the closed diamond) participates in the formation of the substrate-binding pocket. The mutations associated with Hirschsprung's disease are represented by the open triangles. GDNF: glial-derived neurotrophic-factor; MEN: multiple endocrine neoplasia.

the clinical presentation of disease (i.e., whether pheochromocytomas and hyperparathyroidism are likely to be associated with MTC) [20]. Ninety-four percent of patients with MEN-IIB have an identical missense mutation at codon 918 in the tyrosine kinase catalytic domain of *RET* that results in substitution of a threonine for methionine. The *RET* mutation in patients with de novo MEN-IIB arises on the paternally derived allele and is associated with advanced paternal age [21]. The clinically distinct syndrome of FMTC is associated with germline mutations in the extracellular or intracellular portions of *RET*. The structure of the *RET* proto-oncogene with the associated mutations characteristic of MEN-IIA, MEN-IIB, FMTC, and Hirschsprung's disease is shown in Figure 1.

It was immediately apparent that the demonstrated genetic mutations in the *RET* proto-oncogene had great clinical relevance to the treatment of patients with MEN-IIA, MEN-IIB, and FMTC. Kindred members at risk for inheriting one of the disorders could be easily identified by direct DNA testing for the disease-specific mutations. Such testing provided the opportunity to perform prophylactic thyroidectomy (in patients who had inherited a mutation) prior to the development of thyroid disease, evident either by physical examination or by elevated calcitonin levels.

Our group studied 58 children from seven kindreds with MEN-IIA known to be at direct risk for MEN-IIA [22]. The children were evaluated by calcium and pentagastrin provocation with measurement of plasma CT levels, haplotype analysis, and direct DNA testing for mutations in the *RET* proto-oncogene. Twenty-three children were found to have *RET* mutations; thyroidectomy was offered to all of them, but only 13 children and their parents agreed to thyroidectomy. Seven of the children had minimally elevated plasma CT levels following provocative testing; in the other six the plasma CT levels were normal. The 13 children were treated by total thyroidectomy, total parathyroidectomy/parathyroid autotransplantation, and resection of lymph nodes in the central zone of the neck. The disease was confined to the neck in all 13 children, and there were no metastases to 175 cervical lymph nodes. Following thyroidectomy the plasma CT levels were low and did not increase above the normal range following provocative testing. Histologic studies showed that each of the 13 children had C-cell hyperplasia or MTC by standard light microscopy and by immunohistochemical staining. The 13 children have been evaluated 3 years following thyroidectomy, and in each the stimulated plasma CT levels have been unchanged from the values determined immediately postoperatively. It appears, therefore, that prophylactic or early thyroidectomy is curative in family members who have a characteristic mutation in the *RET* proto-oncogene but no clinical or biochemical evidence of MTC. This strategy of prophylactic intervention in patients who have a genetic predisposition for developing MEN-IIA, MEN-IIB, or FMTC can doubtless be applied to other patients who have a genetic predisposition for malignancies such as carcinoma of the breast or carcinoma of the large bowel.

Our current policy is to test children at risk for disease as soon as MEN-IIA or FMTC is detected in their kindred. In this setting children shown to have a characteristic *RET* mutation are advised to have surgery around the age of 5 years. In kindreds with MEN-IIB, children at risk for disease are tested by direct DNA analysis of placental cord blood or blood obtained postpartum. If the characteristic facial features of MEN-IIB are recognized at birth, the child's parents are advised that a thyroidectomy should be performed during the first year of life.

It is important that genetic counselors be closely involved in the study of these patients. They provide a critical role in explaining the genetics of the disease and in helping families understand the reasons specific therapy is recommended. In our clinic genetic counselors are involved in the management of kindreds and interact with them at every stage of evaluation and treatment.

Treatment

It is important to realize that the best treatment for MTC is operative resection. In our experience this malignancy has not responded to standard chemotherapeutic regimens, nor has it been sensitive to conventional doses of external beam radiotherapy.

Thyroidectomy for Patients with Primary MTC

The treatment for patients with MEN-IIA, MEN-IIB, or FMTC is total thyroidectomy and resection of lymph nodes in the central zone of the neck. In our clinic total parathyroidectomy/parathyroid autograft are performed in patients with MEN-IIA. If enlarged lymph nodes are found in the central zone or the lateral neck a modified neck dissection is performed. If a patient with MTC has curable disease at the time of presentation one either wins or loses the battle of cure based on meticulous operative technique and attention to detail. During the thyroidectomy great care must be taken to completely resect the thyroid tumor and involved lymph nodes while preserving the function of the recurrent laryngeal nerves, the external branch of the superior laryngeal nerves, and the parathyroid glands.

It is also important to remember that patients who present with MTC must have the presence of a pheochromocytoma excluded. If a pheochromocytoma is identified it should be removed prior to performing the thyroidectomy.

During the postoperative period patients should have a provocative test to determine if the plasma CT is elevated, indicating the presence of residual MTC. If the postoperative plasma CT is not elevated above the basal level, patients should be followed annually for 5 years. There are no data to indicate that patients should have continued provocative testing 5 years after thyroidectomy if the plasma CT levels have been normal during the intervening years. Also, it is unclear at this point whether early thyroidectomy in children with MEN-IIA or FMTC who have characteristic *RET* mutations require provocative testing on a long-term basis.

Thyroidectomy for Patients with Persistent or Recurrent MTC

More than 50% of patients whose MTC is palpable at the time of diagnosis have evidence of lymph node metastases at neck exploration [23, 24]. Many of these patients have persistent disease, as evidenced by elevated plasma CT levels following thyroidectomy [25, 26]. Although several groups had attempted curative resections in patients with clinical or biochemical evidence of persistent MTC after initial surgery, there were few well documented successes until the report of Tisell and associates [27]. These authors operated on 11 patients with persistently elevated plasma CT levels following thyroidectomy for MTC. They performed a "microdissection" characterized by meticulous resection of the central and lateral lymph nodes in the neck. In four of these patients the basal plasma CT was normal and did not become elevated following intravenous administration of calcium and pentagastrin. Subsequently, Moley and associates [28] reported their experience with reoperations in 45 patients who had persistent or recurrent MTC after thyroidectomy but no evidence of distant disease. Postoperative stimulated plasma CT levels were in the normal range in 17 patients (38%) and were not significantly lowered in 6 patients (13%). It is remarkable that Moley and his colleagues had a low complication rate in their series of patients despite the extensive dissections performed. This is a significant accomplishment and indicates that reoperation is indicated in selected patients with MTC who have not been cured by the initial thyroidectomy. It should be remembered, however, that MTC is often an indolent disease, and patients may live for years with evidence of distant metastases [29].

Future Directions

There continues to be a great deal of interest in MTC, especially when it presents in a familial pattern. The ability to detect kindred members who have inherited MEN-IIA, MEN-IIB, or FMTC and to intervene using prophylactic or early thyroidectomy represents the usefulness of direct DNA testing in patients at risk for a familial cancer. There is great interest in defining the abnormal cellular biochemistry resulting from the genetic mutations. By doing so it may be possible to develop nonsurgical strategies that are preventive in kindred members at risk for MTC or curative in those who have developed early disease.

Résumé

Le cancer médullaire (MTC) de la thyroïde est une tumeur rare qui a suscité beaucoup d'intérêt car il se présente souvent comme une tumeur familiale et il est associé aux syndromes de Multiple Endocrine Neoplasia (MEN) de type 2, I 2A ou 2B et le cancer médullaire familial, le Familial Medullary Thyroïde Carcinoma (FMTC). Les cellules du MTC sécrètent de la calcitonine, une hormone polypeptide qui est un excellent marqueur tumoral, utile pour déterminer la présence de la maladie, soit en préopératoire, soit après thyroïdectomie. La découverte que les mutations du proto-oncogène RET se voyaient dans les syndromes MEN du type 2 a été très important car elle a clairement démontré qu'il existait une corrélation entre le génotype et le phénotype, et plus important, elle a fourni un mécanisme par lequel les membres d'une famille à risque pouvaient être identifiés par analyse directe d'ADN. Presque tous les patients ayant un syndrome MEN 2A, MEN 2B et FMTC développent un MTC, ainsi il est raisonnable de proposer une thyroïdectomie dès lors que la mutation RET a été identifiée. En raison de l'aggressivité des MTC chez les patients MEN 2B, la thyroïdectomie doit être effectuée pendant la première année de la vie alors que chez les patients MEN 2A, ou la tumeur apparaît être plus indolente, on peut attendre jusqu'à l'âge de 5 ans. L'exploration réitérative du cou chez les patients ayant un MTC persistant ou récidivé est efficace chez un nombre important de patients, même si le succès de l'opération nécessite une sélection stricte de patients et une évaluation préopératoire soigneuse. Le cancer médullaire de la thyroïde, faisant partie du syndrome MEN de type 2, représente un excellent modèle pour montrer l'utilité d'une thérapeutique interventionnelle chez les patients où on a mis en évidence une prédisposition génétique au cancer.

Resumen

El cáncer medular (CMT) es un tumor tiroideo no común que atrae mucho interés en virtud de su frecuente presentación como tumor familiar y su presencia en los síndromes de neoplasia endocrina múltiple (NEM) tipo 2, NEM 2A y NEM 2B, y el carcinoma medular familiar de tiroides (CMFT). Las células tumorales del CMT secretan calcitonina, una hormona polipeptídica que sirve como excelente marcador tumoral para establecer la presencia de la enfermedad, bien sea preoperatoriamente o luego de tiroidectomía. El descubrimiento de que las mutaciones en el protooncogen RET se asocian con los síndromes NEM2 fue de alta significación por cuanto demostró una clara relación entre genotipo y fenotipo y, lo más importante, aportó un método mediante el cual se pueden identificar los familiares en riesgo por el análisis directo de ADN. Virtualmente, todos los pacientes con NEM 2A, NEM 2B y CMFT desarrollan CMT y, por lo tanto, hay clara indicación de practicar tiroidectomía tan pronto como se haya identificado la mutación RET. Puesto que el CMT parece ser mucho más agresivo en pacientes con NEM 2B, en este contexto se debe practicar la tiroidectomía en el primer año de vida, en tanto que en los pacientes con NEM 2A, donde el tumor es más indolente, se puede aplazar la tiroidectomía hasta la edad de cinco años. La exploración reoperatoria en pacientes con evidencia de CMT persistente o recurrente ha probado ser efectiva en un número significativo de pacientes, aunque el éxito de la operación

requiere una cuidadosa selección y una meticulosa valoración preoperatoria. El CMT, tal como aparece en los síndromes NEM2 representa un excelente modelo que ilustra la utilidad de la terapia intervencionista en pacientes en quienes se demuestre una predisposición genética al cáncer.

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