8.1. DIAGNOSIS AND MANAGEMENT OF MEDULLARY THYROID CARCINOMA

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Medullary thyroid carcinoma (MTC) arises from thyroid C cells that secrete calcitonin (CT). It accounts for only about 5% of thyroid carcinomas in the United States (Hundahl 1998), but has aroused considerable interest because of its distinctive biochemical, genetic and clinical features. Although this is usually a sporadic tumor, some are familial tumors that occur as a result of autosomal dominant genetic mutations in the RET protooncogene that produce unique clinical syndromes (Dunn 1993). The explication of the genetic basis of MTC has revolutionized management of the familial form of this tumor and has provided insight into its pathogenesis and clinical behavior. In this chapter we review the important clinical characteristics, hereditary and sporadic forms of the disease, and its biochemical and molecular diagnosis, treatment and follow-up. Several recent publications summarize the major advances in this field, (Eng 1996; Machens 2003b; Massoll 2004) and the Seventh International Workshop on Multiple Endocrine Neoplasia held in Gubbio, Italy in 1999 provides some consensus on the diagnosis and therapy of familial MTC (Brandi 2001), although major questions remain concerning the timing of thyroidectomy in certain gene carriers.

PATHOLOGY
C-cell Hyperplasia and MTC

RET germ-line mutations in humans affect four major types of tissues that originate from neural crest cells: thyroid C cells, parathyroid cells, chromaffin cells of the adrenal medulla, and enteric autonomic plexus (Eng 1996). MTC, which arises from thyroid
C cells, is mainly found in the upper third of the thyroid lobes. In familial disease, this is the site of its first identifiable manifestation: C cell hyperplasia (CCH), which is a precursor of familial MTC that progresses to microscopic MTC (Modigliani 1998). The progression of CCH to MTC occurs at different rates depending on the RET mutation (Machens 2003b). Hereditary MTC is thus bilateral and multicentric, whereas sporadic MTC is generally manifest as a single thyroid tumor (Beressi 1998; Bachelot 2002).

A wide spectrum of histologic patterns may be seen with MTC. Although lymph node metastases are rarely present when MTC is diagnosed early by genetic screening (Wells Jr 1994), they are almost always present when the tumor is palpable, whether it is sporadic or familial MTC. The tumor typically metastasizes to lymph nodes in the central and lateral cervical compartments, to mediastinal lymph nodes, or to the lung, liver or bone.

In fine-needle aspiration (FNA) cytology samples, MTC cells may appear cuboidal, spindled or plasmacytoid. MTC tends to be over-diagnosed by cytology because it may mimic a variety of benign and malignant entities and should therefore be confirmed by immunohistochemical staining for CT.

CCH is usually diagnosed when more than 6 C-cells are seen per thyroid follicle and/or more than 50 intrafollicular CT-positive cells are seen in at least one low-power (100x) field. CCH can be confirmed by a immunohistochemical reaction for CT and can range in appearance from mild to diffuse CCH, which can develop into nodules that replace preexisting follicular epithelium (Hinze 1998). The transition from benign CCH to invasive MTC is marked by disruption of the follicular basement membrane by C-cells. Familial tumors undergo a transition from a RET mutation that leads to early clonal C-cell expansion, which then proceeds to transformation from neoplastic CCH to MTC, and eventually to lymph node and distant metastases, all proceeding at strikingly different rates with different RET mutations (Machens 2003a, 2003b).

**HORMONAL ACTIVITY OF MTC**

MTC secretes several proteins in addition to CT, including ACTH, CEA, histamines and vasoactive peptides, but clinically the most important is CT, which serves as the major clinical marker for the tumor. In fact, plasma CT levels correlate closely with MTC size (Engelbach 2000), especially in familial cases, and preoperative CT levels <50 pg/mL predict postoperative normalization of CT (Cohen 2000).

**SURVIVAL RATE OF PATIENTS WITH MTC**

The 10-year survival rate of patients with MTC ranges from about 50% to 80%, and averaged 75% in over 2,000 cases of MTC in a national cancer database with 53,856 cases of thyroid carcinoma treated in the US between 1985–1995 (Hundahl 1998). Survival rates are tightly linked to early diagnosis and tumor stage, and vary significantly among patients with sporadic and familial MTC (Cohen 2000; Brandi 2001). Early thyroidectomy has lowered the mortality rate of hereditary MTC to less than 5%, well