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REVIEW

Surgical management of sporadic medullary thyroid cancer

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Calcitonin

Summary Inherited and sporadic medullary thyroid cancer (MTC) is a rare carcinoma. Sporadic MTCs represent 70% of cases. Diagnosis is currently made with the routine use of serum calcitonin (CT) measurements to screen patients with nodular thyroid disease. Surgery is the only curative treatment of MTC and since cervical lymph nodes metastases are frequent and can occur at an early stage, a standardized lymph node dissection should be associated to total thyroidectomy. However, the extent of lymphadenectomy remains debated. Prognosis of MTC is related to both the stage of the disease and the extent of initial surgery. When tumor remnants persist after surgery, there are very few therapeutic alternatives, and these are generally of limited curative value.

Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine tumor originating from thyroid C cells and secreting calcitonin (CT) (Figs. 1—3). This type of tumor is rare: 0.2 to 0.4% of all patients with thyroid nodules [1—5] and between 5 and 10% of thyroid cancers. Prognosis is good with survival at 5 years of 86% and at 15 years of 70% [6,7], but depends in individual patients on the stage and size of the tumor as well as the quality of the initial surgical management. Thanks to widespread laboratory screening of serum calcitonin levels (CT), the proportion of MTC detected at the stage of microcarcinoma ($\leq$ 10 mm in largest diameter) has increased. Early detection has improved the rate of cure that ranges from nearly 100% for MTC whose diameter is only a few millimeters in diameter to 90% for tumors less than 10 mm and 50% when greater than 1 cm [8]. However, early diagnosis is not enough to guarantee a low recurrence rate: initial surgery should be adapted to the tumor.

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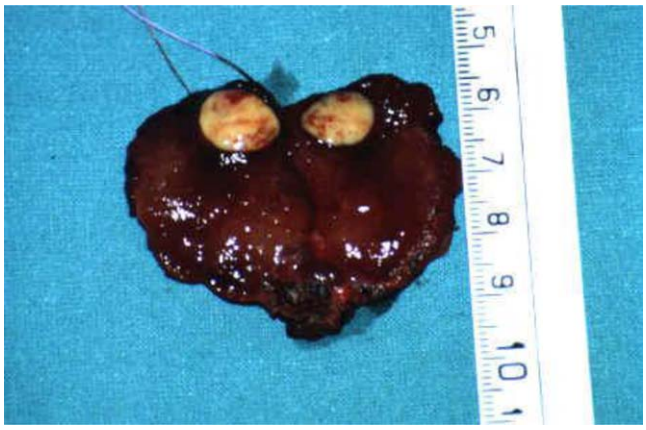

Figure 1. Specimen showing medullary thyroid cancer at upper pole: yellowish, well-limited nodule with soft-to-firm consistency.

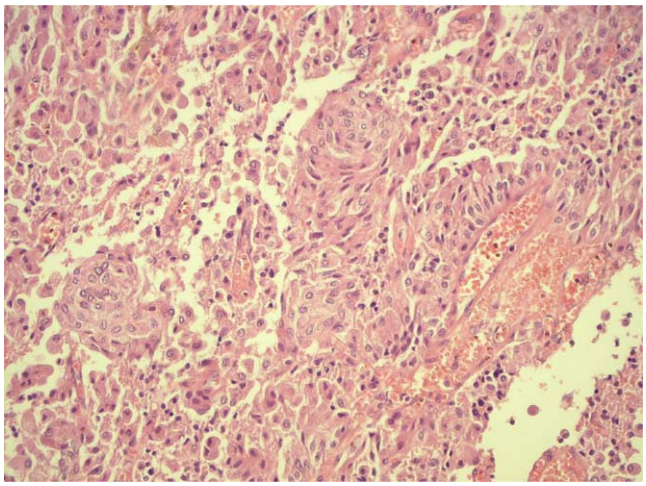

Figure 2. Histopathology of medullary thyroid cancer (hematoxylin and eosin stain): round, polyhedral or spindle cell proliferation, with eosin cytoplasm, arranged in sheets and clumps.

Because MTC is classically characterized by extremely early lymphophilic dissemination while the potential for distant metastases (liver, lung, bone) is low, the goal of this paper was to review the current indications for extended thyroidectomy and lymph node (LN) dissection in MTC.

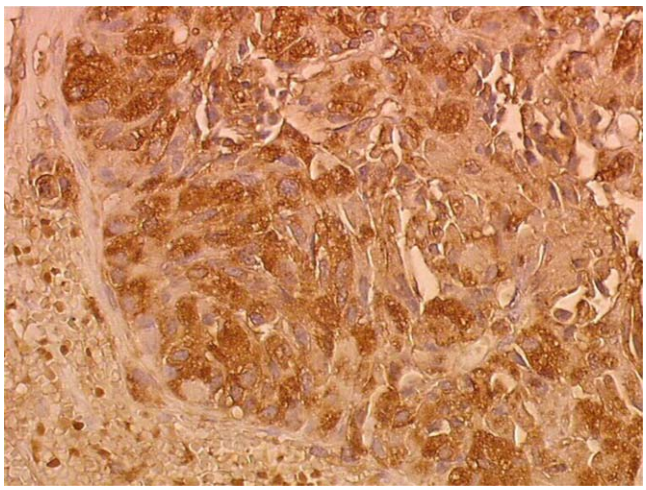

Figure 3. Histopathology of medullary thyroid cancer (immunochemistry): cytoplasmic C-cell tagging with anti-calcitonin antibodies.

MTC is sporadic in 65 to 70% of cases, and inherited in 30 to 35%. Inherited MTC's belong either to types 2a or 2b multiple endocrine neoplasia (MEN) syndromes or are isolated. Management of inherited MTC is particular. Herein we will deal with sporadic MTC only.

Diagnosis

Calcitonin dosage

Most cases of sporadic MTC are detected through routine measurement of CT. In 20% of cases, MTC is discovered after work-up for enlarged cervical LNs or, more rarely, by a clinical syndrome associating flush and diarrhea attesting to CT hypersecretion in multimetastatic MTC. MTC can also be discovered by chance either on a thyroidectomy specimen performed for a nodule or because of an elevated carcinoembryonic antigen (CEA) level obtained for surveillance of another cancer, i.e., colon cancer.

The mean level of CT, classically less than 10 pg/ml, varies according to gender, rising to 16 pg/ml in men and 8 pg/ml in women. Higher levels of CT are sensitive and specific markers of MTC and a serum CT level greater than 100 pg/ml is diagnostic when associated with a thyroid nodule. High preoperative CT levels in a patient scheduled for thyroidectomy should lead to carcinologic resection with curative intent. Karges et al. [9] recommend CT dosage in all patients with thyroid nodules; if the CT level is greater than 10 pg/ml in a patient without renal insufficiency and who is not taking PPI's, a pentagastrin stimulation test should be performed. If after stimulation, CT is greater than 100 pg/ml, the risk of MTC is higher than 50%. Costante et al. [10] reported that the positive predictive value (PPV) of baseline CT for the diagnosis of MTC was 8% when CT was between 20 and 50 pg/ml, 25% when between 50 and 100 pg/ml, and 100% when CT was greater than 100 pg/ml. Moderate elevations of CT (< 100 pg/ml) can also be seen in other diseases, benign or malignant, such as C-cell hyperplasia (CCH), small cell pulmonary cancer, carcinoid tumor, or chronic renal failure (CRF) (10% of patients with CRF have a CT greater than 30 pg/ml [11]). PPI treatment resulting in hypergastrinemia and smoking, through the intermediary of nicotine, is also known to stimulate CT secretion [12]. The pentagastrin stimulation test could be of diagnostic interest in these cases but it is no longer available in France. CT stimulation with high dose calcium gluconate could solve the problem of patients with intermediate CT levels [13], but this test is not performed routinely. The diagnostic and therapeutic rationale is therefore to rely on basal CT levels, which, when superior to 30 pg/ml, are highly predictive of MTC; this should be used as a threshold value leading to total thyroidectomy with extended LN dissection [14].

Laboratory testing should be completed by measurement of CEA; this tumor marker is neither sensitive nor specific, but constitutes a good reflection of the tumoral mass and allows long-term patient follow-up, particularly in the metastatic forms of MTC.

Place of fine needle aspiration cytology and frozen section

MTC can be diagnosed through fine needle aspiration (FNA) cytology when anti-CT immunomarkers are positive, but this investigation is not as reliable as baseline serum CT levels (Figs. 1—3). The sensitivity of FNA cytology is 63% [15]