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Review Article

Differentiated Thyroid Carcinoma Associated with Hyperthyroidism

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Abstract

Hyperthyroidism should lead to a lower incidence of thyroid cancer than that observed in euthyroid patients. Thyroid cancer associated with thyrotoxicosis is rare and poorly recognized, which may result in delayed diagnosis, inappropriate treatment and even poor prognosis. Thyroid carcinoma can be associated with autonomously functioning thyroid adenoma, toxic multinodular goiter, or Graves' disease. The etiology, pathogenesis, diagnosis and treatment of this challenging setting were systematically reviewed in order to provide a comprehensive guidance for clinicians. Medical history, biochemical assessments, radiobiological imaging, and ultrasonography-guided fine-needle aspiration combined with pathological examinations were found to be critical for precise diagnosis. Surgery remains a mainstay of treatment for both pathologies. This study summarizes the current evidence regarding the association of thyroid cancer with thyrotoxicosis and whether this affects the patient outcome.

ABBREVIATIONS

TMG: Toxic Multinodular Goiter, GD: Graves' Disease, TSHR: TSH Receptor, TRAb: Thyrotrophic Receptor Antibodies, T3: Triiodothyronine, T4: Thyroxin, TSH: Thyroid-Stimulating Hormone, US: Ultrasonography, FNA: Fine-Needle Aspiration, US-FNA: Ultrasonography-Guided Fine-Needle Aspiration, DTC: Differentiated Thyroid Carcinoma, PTC: Papillary Thyroid Carcinoma, MTC: Medullary Thyroid Carcinoma

INTRODUCTION

In practice, thyroid cancer is typically present with thyroid or clinical/subclinical hypothyroidism. In theory, thyrotoxicosis with suppressed TSH should lead to a lower incidence of thyroid cancer than that observed in thyroid patients. The prevalence of thyroid carcinomas found during surgery in hyperthyroid patients, is reported to vary widely, reaching up to 21.1% [1-17]. This is probably due to multiple factors, including the cause of hyperthyroidism, the different criteria for choosing surgery, the extent of thyroidectomy (lobectomy or total thyroidectomy), and the geographical variation in the incidence of thyroid cancer in general and the extent of histological examination of the removed thyroid tissue. To further complicate the matter, discrepancies appear not only in reports on the incidence but also on the aggressiveness of thyroid cancer associated with hyperthyroidism. For instance, while some reports describe the cancer as very aggressive, often invasive, and metastatic to regional lymph nodes, even when the primary tumor is small and possibly fatal; in other series the clinical course was not different from thyroid patient. Up to this date the reasons for these discrepancies have not been solved and the incidence and aggressiveness of thyroid cancer remain controversial [7-12,15-20]. All histological types of thyroid cancers can be associated with all types of hyperthyroidism, although the most frequently reported type is Papillary Thyroid Carcinoma (PTC), followed by follicular thyroid carcinoma [21-24], and rarely by anaplastic carcinoma and Medullary Thyroid Carcinoma (MTC) [1,6,25].Thyroid carcinoma, however, is usually identified by Ultrasonography (US) [26,27] and then confirmed by Ultrasonography-Guided Fine-Needle Aspiration (US-FNA) followed by pathological examinations. Most carcinomas are small in size and the majority is micro carcinomas. In many cases thyroid cancer is not known preoperatively, but it is found incidentally during postoperative histologic examination of the thyroid. No significant differences were found in clinical characteristics at presentation between coincidentally discovered thyroid cancers and preoperatively known clinical cancers [28-31]. However, some authors [32] reported that, the diagnosis of incidental thyroid carcinoma in patients who were operated on for a benign disease was more frequent in thyroid patients than in patients with hyperthyroidism. It has been reported that thyroid cancer is diagnosed more frequently in patients with Graves' Disease (GD) [28-30,33-48] than in patients

with uninodular toxic goiter [48-58] or Toxic Multinodular Goiter (TMG) [1,2,59-62], whereas other studies presented the same results for GD, but slightly higher carcinoma prevalence within hot nodules and TMG. Surgery remains a mainstay in both cancer elimination and control of thyrotoxicosis.

The objective of this paper was to summarize current evidence regarding the association of thyroid cancer with autonomously functioning thyroid adenoma, toxic multinodular goiter, or Graves' disease, and whether this affects the patient outcome.

Thyroid Cancer in Patients with Autonomous Adenoma

Most autonomously functioning thyroid nodules are benign follicular neoplasms but rarely patients with toxic adenoma may harbor thyroid cancer in the autonomously functioning nodule [45-58]. The reported probability of a hot nodule being associated with malignancy (i.e., a thyroid carcinoma in or outside the hot nodule) ranges between 1 and 44%. These mainly involve papillary and less often follicular or Hurtle histological types. However, hot nodules in children seem to carry a higher risk of malignancy of up to 29% of thyroid carcinomas within the hot nodules. The true incidence of thyroid cancer in patients with autonomous adenomas may be underestimated because occasionally large doses of radioiodine are used to treat such cases if they do not undergo surgery, which may be sufficient not only to cure the thyrotoxicosis but also the cancer. There are reports of malignant hot nodules in which activating mutations of the Thyrotrophic Receptor (TSHR) gene were identified. Functional analysis of some reported TSH receptor mutations revealed that only the hot thyroid carcinomas with the TSHR mutations M453T, I486F, L512R, F631I, T632A, T632I, D633H and D633Y were associated with constitutively activating TSHR mutations [8,12,57].

Thyroid Cancer in Patients with TMG

Whereas carcinomas, largely of the papillary type, occur in nontoxic nodular goiters with a reported frequency of 4-17% of cases, the reported incidence of thyroid cancer in patients with TMG ranges between 1.8-8.8% [1,2,7,8,59-62]. However, the data available in the literature regarding the incidence and the evolution of the disease are controversial. Some authors found no significant difference for the incidence of thyroid cancer between toxic and nontoxic multinodular goiter. In another study, lymph node involvement was found in 23% of the cases with TMG and cancer. In a third one, no lymph node metastases were detected although distant metastases were found in some cases. Pathogenesis of cancer in mutinodular goiter was related to the extracellular growth factors, such as transforming growth factor β and IGF-1, stimulating growth and dedifferentiation of thyroid epithelial cells, leading to tumor genesis. Ultrasonography detects solid thyroid nodule with intraocular hyper vascularization. US-FNAC should be focused on lesions, which appear suspicious by US features, and not on larger or clinical dominant nodules. In the cases of nodules that show suspicious features and when it is not possible to exclude the possibility of malignancy by FNAC, the preferred choice of treatment should be surgery [26-28]. Computed Tomography Scan (CT scan) provides not only the information of nodule size, calcifications and compression of the adjacent tissue, but also the metastases of lymph nodes, lungs and bones. Magnetic resonance imaging is thought to be more precise than CT in the anatomy-topographic evaluation of the sub sternal goiter. Thyroid scan with 99mTc-pertechnetate presents functioning thyroid nodule with minimal uptake of the rest gland. Hence, if US suggest malignant signs such as calcifications and vascularity, FNAC of primary nodule should be recommended. Surgery is the first choice because it can resect the primary tumor and resolves compression and thyrotoxicosis symptoms [1,2,7,8,12,59,60].

Thyroid Cancer in Patients with GD

The prevalence of concomitant thyroid cancer occurring in patients with GD reaches up to 17%. It appears that thyroid nodules in Graves' goiters have a greater risk of malignancy [3,6,14,26,33-43]. The incidence of thyroid carcinoma associated with GD varied from 0.5 and 15.0%. This incidence varied from 15% to 45.8% if patients with a nodule were considered [8,12,30,43]. Graves' disease is an autoimmune disease that results from stimulation of the TSH Receptor (TSHR) by Thyrotrophic Receptor Antibodies (TRAb). Increased TRAb is helpful in distinguishing GD from other etiologies of thyrotoxicosis. Radioactive iodine uptake is an alternative testing, which is usually elevated. Thyroid scintigraphy is an important test in the evaluation of patients with GD and nodules, and the prevalence of thyroid cancer in a cold nodule provides justification for further diagnostic evaluation. Although PTC is the most frequently reported histologic type occurring in GD, MTC with concomitant GD has also been reported [24]. A Thyroid scan shows a diffused radioisotope uptake; whereas the tumor shows generally low or no uptake as a 'cold' nodule. Ultrasonography may be particularly useful through providing representative information of GD with diffuse, bilateral or isthmic goiter, heterogeneous and hypo echogenicity parenchyma, hyper vascularization, and describing the characteristics of malignant thyroid nodule, extra thyroidal extension, and guided FNA cytology/biopsy of nodules. Fine-needle aspiration cytology from nodules, which are found in patients with GD, can cause diagnostic difficulties because the cytomorphologic changes in this disease as a consequence of ant thyroid drug treatment may mimic features of papillary thyroid carcinoma. Furthermore, atypical produced by the administration of radioactive iodine may be severe, leading to an erroneous diagnosis of malignancy. In a recent study nuclear elongation, pale powdery chromatin, intranuclear grooves, and small eccentric nucleoli were found to be significant for the diagnosis of papillary thyroid carcinoma arising in GD [8,12]. Thyroid cancer associated with GD is found more commonly in surgically treated patients (2.5%) than in patients after radioactive iodine therapy (0.17%). Most carcinomas associated with GD are small and are found incidentally during postoperative histological examination of the thyroid (up to 88.0%). Patients with micro carcinomas and concomitant GD and thyroid patients with cancers of

equal size have an excellent prognosis and longer disease-free survival. The overall frequency of incidentally found carcinomas in Graves' patients undergoing surgery varied from 3.33% to 4.2% and that of clinically important thyroid carcinomas varied from 3.3% to 4.7% [29,30]. It has been reported that, thyroid carcinoma concurrent to GD is usually aggressive and metastatic to regional lymph nodes, even when the primary tumor is small and that it has a worse clinical outcome compared to thyroid patients with differentiated thyroid cancer. Lymph nodes involvement was found in up to 61.5% of the patients and the incidence of locally advanced cancers was significantly higher in older patients. In Graves' patients, carcinomas are found to be larger, more often multifocal, locally invasive and more often metastatic to distant sites than in patients with hot thyroid nodules. However, some studies report discordant results or do not highlight the aggressive characteristics of thyroid carcinomas in GD [30,34,35,38]. Prospective studies with a large number of patients could give clear answer about the aggressiveness of thyroid cancer in GD. The possible reasons that could explain the increased frequency and aggressiveness of clinical thyroid cancer reported by some studies for patients with GD are not clear. Thyroid Stimulating Hormone (TSH), by binding to the Thyroid-Stimulating Hormone Receptor (TSHR), and probably multiple other factors, affect the evolution of thyroid cancer. Neoplastic cells of differentiated thyroid cancer, like normal thyroid cells, express functional receptors for TSH. In Graves', antibodies (TSAbs) are produced that have strong agonistic activity to the TSHR, and this results in antibody-mediated stimulation of the receptor. Stimulation of TSHR by antibodies leads to secretion of thyroid hormone and hyperthyroidism independently of the hypothalamic-pituitary-thyroid axis. Moreover, TSAbs might play a role in stimulating thyroid cancer growth, invasiveness and angiogenesis by up regulating the vascular endothelial growth factor, placenta growth factor, and their receptors. TSAbs use the same signaling pathways that are used by TSH for cell activation and growth. Taking into consideration that chronic TSH stimulation affects the prognosis of thyroid cancer it could be postulated that the TSH mimicking effect of TSAbs could explain the increased aggressiveness of thyroid cancer in Graves' patients. Apart from that, different growth factors that probably are produced by the over stimulated, by TSAbs, and hyper vascularized thyroid could affect as well the growth and metastases of thyroid cancer in Graves' patients. Considering the important functional similarities between TSH and TRAb, IGF-1 could also affect the growth of Differentiated Thyroid Carcinoma (DTC) in patients with GD. Surgery is the most appropriate treatment for GD with concomitant DTC. Near-total or total thyroidectomy is now well established as the choice in patients undergoing surgery for GD. In addition, cervical lymph nodes are dissected when macroscopically involved [1]. However, surgery for GD is recognized to be more challenging due to the increased vascularity of the thyroid gland and has been reported to be associated with higher rates of complications compared with surgery for other benign thyroid conditions. Since thyroid storm may be precipitated by the stress of surgery, anesthesia or thyroid manipulation, pretreatment with anti-thyroid drugs with or without beta-adrenergic blockade is recommended. In addition, corticosteroids, and potentially cholestyramine can be used to rapidly prepare for emergent surgery [8,12]. Potassium iodine has been used to attenuate organification and release of thyroid hormones as well as thyroid vascularity and intraoperative blood loss during thyroidectomy [3,6,8].

CONCLUSIONS

Patients with a toxic nodule or TMG usually undergo thyroid ablation soon after the diagnosis. Evaluation of the malignancy risk of a nodule in patients with GD appears to be crucial. For GD associated with DTC, surgery after controlling thyrotoxicosis with medications remains the first choice. Thyroidectomy should be the choice of treatment in patients with GD and suspicious nodules. It is important to perform thyroid and neck US and US-FNAC prior to radioiodine therapy or thyroidectomy, in order to detect thyroid cancer.

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