

Hyperthyroidism with concurrent thyroid cancer



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Several studies have been conducted to evaluate the clinical relevance of the association between malignancy and hyperfunction of the thyroid gland. Although the results of these studies show some discrepancies, they indicate that the coexistence of hyperthyroidism and thyroid cancer cannot be considered a rare finding (1-5). With the aim of assessing the clinical relevance of this association, we have analyzed the incidence and outcome of thyroid cancer in thyrotoxic patients treated by surgery.

Patients and Methods

This was a retrospective review of 202 patients affected by hyperthyroidism, seen and treated at our institutions. There were 54 men (26.7 per cent) and 148 women (73.2 per cent) of age 22-88 (mean 53.5) years. No one had a positive history of X-ray external radiation. Prior to surgery all patients underwent 131. I thyroid scan and sonographic evaluation; thyroid function was assessed by measuring TT3, TT4 and TSH and, in some of them, the response of TSH to the administration of TRH was also evaluated. A preoperative euthyroid state was achieved by methimazole therapy and administration of Lugol's solution before surgery. Thyroid surgery consisted in sub-total, near-total or total thyroidectomy for the treatment of toxic diffuse goiter and toxic multinodular goiter, while for toxic adenoma the treatment of

Abstract

The occurrence of thyroid malignancy is considered a rare event in hyperthyroid patients. With the aim of assessing the clinical relevance of this association, we have analyzed the incidence of thyroid cancer in hyperthyroid patients treated by surgery.

The incidence of thyroid cancer was retrospectively evaluated in 202 hyperthyroid patients who underwent thyroidectomy during a twenty-year period.

A thyroid cancer was diagnosed in 12 cases (5.9 per cent). Histologic examination revealed the presence of papillary carcinoma in 9 cases, follicular carcinoma in 1 case and Hürthle cell carcinoma in 2 cases. The association between thyroid cancer and hyperthyroidism was more frequent in toxic adenomas (17.8 per cent) than in toxic diffuse (5.3 per cent) or multinodular goiters (1.7 per cent). In 8 patients they presented as an occult carcinoma (maximum diameter below 1 cm), but unfavourable histologic features, such as local invasiveness and multifocality, were found in 5 of them. Follow-up data indicate that all 12 patients are currently alive and apparently free of disease.

Hyperthyroid patients, particularly those affected by toxic adenomas, should be carefully evaluated to exclude the presence of concurrent malignancy. A special attention should be made moreover to the presence of "occult" lesions that, in our study was characterized in a higher proportion (62.5 per cent) of cases, by unfavourable histologic features.

Key words: Hyperthyroidism thyroid cancer.

Riassunto

IPERTIROIDISMO COESISTENTE AL CANCRO DELLA TIROIDE

La frequenza di patologia tiroidea maligna si riscontra raramente in pazienti ipertiroidi. Abbiamo analizzato l'incidenza di cancro tiroideo in pazienti ipertiroidi trattati chirurgicamente con lo scopo di valutarne gli aspetti clinici. L'incidenza di cancro della tiroide è stata studiata retrospettivamente in 202 pazienti ipertiroidi sottoposti a tiroidectomia in un periodo di 20 anni. Il cancro della tiroide fu diagnosticato in 12 casi (5,9%). In 9 casi l'esame istologico rilevò la presenza di carcinoma papillare, 1 caso di carcinoma follicolare, 2 casi di carcinoma di Hürthle. L'associazione tra cancro della tiroide ed ipertiroidismo era

più frequente nell'adenoma tossico (17,8%) che in quello diffuso (5,3%) o nel gozzo multinodulare (1,7%). Su 8 pazienti con carcinoma occulto (diametro inferiore ad 1 cm), 5 presentavano aspetti istologici sfavorevoli come invasività e multifocalità. Il follow-up rileva che 12 pazienti sono sopravvissuti e non hanno avuto recidive.

Il paziente ipertiroidico, deve essere esaminato con scrupolo per escludere la presenza di patologia maligna. Particolare attenzione meritano le lesioni occulte che nel nostro studio rappresentano la più alta percentuale dei casi (62,5%).

Palore chiave: Ipertiroidismo, cancro.

choice was a lobectomy alone or associated with histomusectomy, except for those cases in which the contralateral lobe presented clinically or sonographically detectable nodules or was considered pathologic at surgery. In 2 cases thyroid surgery was complicated by the occurrence of acute hypoparathyroidism, and no permanent lesion of the laryngeal nerve was observed. The histologic specimens were reexamined by two experienced pathologists according to the standard approach published by Rosai (6) and thyroid neoplasia was diagnosed according to the WHO classification criteria; histopathological diagnoses were graded according to the thyroid malignancy TNM age related classification (7). Patients were followed up for a mean period of 7.5 years and they are currently all alive and apparently free of disease.

Results

Of the 202 patients examined 41 had toxic adenoma, 123 had toxic multinodular goiter and 38 had toxic diffuse goiter. The presence of thyroid cancer was observed in 12 patients (5.9 per cent), 11 being females and 1 male. Their mean age was 54.8 years (range 35-70). According to widely accepted histologic criteria (7) they were classified as papillary carcinoma (9 cases), follicular carcinoma (1 case), and Hürthle cell carcinoma (2 cases).

In the group of 41 toxic adenomas a thyroid cancer was found in 8 cases (20.2 per cent): 7 females and 1 male. Histologic examination revealed the presence of a papillary thyroid carcinoma in six cases, and a Hürthle cell carcinoma in the remaining two cases. In six cases the lesion presented a maximum diameter below 1 cm. In 3 of these cases more than one tumoral focus was observed. In two patients the hyperfunctioning nodule was the only nodular lesion detectable by palpation or by ultrasound examination. Histological signs of initial invasiveness of the surrounding tissue were evident in a bifocal occult papillary carcinoma partly localized inside the hyperfunctioning nodule. This patient underwent a second stage operation that consisted in the complete removal of all thyroid tissue remaining after the first par-

tial surgical excision and another tumoral focus was identified in the functionally suppressed right lobe. In another patient a papillary carcinoma was present in the same lobe but outside the toxic adenoma.

In six patients multiple clinically or ultrasonographically detectable nodules were associated to the toxic adenoma. In one of them an occult papillary carcinoma was again detected inside the hyperfunctioning nodule; in a second patient a bifocal Hürthle cell malignant lesion also occurred inside the toxic adenoma as well as evident area in the context of a non-functioning nodule localized in the contralateral lobe. In two patients the carcinomatous lesion corresponded to solid non-functioning nodules, measuring respectively 2 and 1.5 cm of diameter while further two cases referred to two occult papillary carcinomas, detected in the contralateral lobe after its removal because of the presence of multinodularity.

Of the 119 patients with toxic multinodular goiter only 2 (1.7 per cent) presented a coexisting thyroid papillary cancer. In one patient the lesion was multifocal, affecting both the right and left lobes and the maximum diameter of tumoral foci ranged from 0.5 to 0.8 cm. Histologic examination revealed the presence of local invasiveness and, considering the age of the patient, the clinical stage of this tumor was the most advanced among all patients studied. In the other case a thyroid carcinoma of 3 cm was detected but no data regarding its relationship with the hyperfunctioning nodules were available.

Thyroid cancer was found in 2 (5.3 per cent) out of 38 patients treated by surgery for a toxic diffuse goiter. In one patient preoperative evaluation demonstrated the presence of a diffusely enlarged thyroid gland without any clinically palpable nodule. Bilateral ophtalmopathy was present and patient was clinically thyrotoxic. The level of circulating antimicrosomal antibodies was markedly high (1:25000). Thyroid scan did not show any cold area and sonographic examination did not identify any nodular abnormality. The patient was operated because of the dramatic increase (more than four times) in the thyroid volume. Histologic examination revealed the presence of three foci of papillary carcinoma, two localized in the right lobe with a maximum diameter of 0.6 and 0.4 cm, respectively and one measuring 0.2 cm in the left lobe. The other patient was treated with repeated cycles of methimazole for six years and underwent thyroidectomy only after the detection of a solid cold nodule with a maximum diameter of 3 cm that, at final histology, was proved to be a follicular thyroid carcinoma.

Discussion

The incidence of thyroid cancer in thyrotoxic patients is extremely variable. Genetic and environmental factors such as the amount of iodine intake may be responsi-

ble for this variability (8,9). The different criteria adopted in the surgical selection of the patients and the consequent different extension of the surgical resection may also contribute to the observed discrepancy. Shapiro et al. (10), for example, found an incidence of thyroid cancer 8.7 per cent among a population of 172 thyrotoxic patients, because a total thyroidectomy was performed in all patients. By using this surgical approach the possibility to find an incidental occult carcinoma, which is known to occur in the general population with an incidence ranging between 0.45 per cent and 35.64 per cent (11,12), may obviously increase, thus leading to, an higher rate of association. In our series of hyperthyroid patients, treated by surgery, a carcinomatous lesion under 1 cm of diameter was detected in 8 cases with a percentage (3.96 per cent) that is similar to the value of 3.6 per cent observed on autoptical material in Italy by Pingitore et al. (13) in a non endemic region, but differ from that of 10.65 per cent reported by Autelitano et al. (11) in different regions, including areas of endemic goiter. It should be noted that half of the occult carcinomas were detected in patients submitted to total thyroidectomy. Another factor that may influence the interpretation of the results is represented by previous therapy with external X-rays, performed for other illnesses. In this regard none of our patients had a positive history for external radiation prior to thyroid surgery.

A high percentage (20.2 per cent) of thyroid carcinoma associated with toxic adenoma has been observed in our patients. The first evidence of the association between thyroid carcinoma and toxic adenoma was reported by Molnar in 1958 (14).

This association has been considered rare with only 50 cases reported in the literature up to 1974 (4); more recent studies have reported an incidence of thyroid carcinoma in patients with autonomously functioning thyroid nodule that appears extremely variable.

It should be noted that while in some study (15,16,17) only solitary toxic adenomas were considered, in others (18,19,20) the incidence of thyroid carcinoma was calculated among patients with autonomously functioning thyroid nodules that not necessarily were hyperthyroid. In another study (21) only children and adolescent patients were examined.

The analysis of the relationship between the localization of the tumor and that of the toxic adenoma shows these different possibilities:

- more frequently, thyroid cancer is present in the functionally suppressed thyroid tissue (20). In this case it is usually considered an incidental finding consisting in an occult lesion. In our experience thyroid carcinoma was most frequently localized outside the toxic adenoma (62.5 per cent), in the functionally suppressed tissue although in three cases, was present in the same lobe.
- sporadically thyroid carcinoma is embedded in, or adjacent to the hyperfunctioning thyroid adenoma (14). In

these cases two distinct cell populations, characterized by a different growth, differentiation and functional behaviour, are present in the same nodule. In some cases the thyroid carcinoma could be localized in a cold area inside the autonomous lesion (22). This observation is very important from a clinical point of view since not all the cold areas inside a “hot” nodule should be attributed to tissue degeneration or necrosis. However among our three patients that presented a thyroid carcinoma in the context of an “hot” nodule the thyroid scan failed to detect cold areas, being their maximum diameter (0.5 cm) under the detection limit of the technique. It would be also interesting to analyze the different oncogenic profile of the two cells populations in order to better understand the molecular pathogenesis of thyroid cancer arising in the context of a differentiated thyroid lesion.

- Exceptionally the whole thyroid tissue of a toxic nodule may be carcinomatous (23,24). Cancer cells are generally considered non functioning but some evidences indicate that thyroid ormonogenesis may indeed occur (25), thus leading to thyroid hormone synthesis and secretion and, rarely, even to hyperthyroidism. However, the presentation of a thyroid carcinoma masquerading as an autonomously functioning thyroid nodule is very rare and needs to be carefully evaluated since many of such cases failed to be included in this category when clinical and histopathologic data were accurately reviewed (26,27).

In patients with toxic multinodular goiter we found a 1.7 per cent rate of associated malignancy, which is similar to that reported in other studies (28). The reason for this lower incidence of thyroid cancer in comparison to that observed in toxic adenomas remains unexplained both from a clinical and biological point of view.

Although the prevalence of thyroid carcinoma in Graves' disease has been examined by many authors (10,29,30), the clinical relevance of this association still remains controversial. In the study of Dobyns et al. (3) only 86 thyroid carcinomas, were found in 34 684 hyperthyroid patients, with an overall incidence of 0.2 per cent. In this multicentric study there was no difference between the incidence of thyroid cancer in patients with Graves' disease and those with toxic adenoma undergoing thyroidectomy (0.4 per cent and 0.3 per cent, respectively). In contrast to these results, thyroid carcinoma has been recently found with a 2.5-fold greater frequency in patients affected by Graves' disease than in patients with toxic adenoma (2). In patients with Graves' disease a more aggressive behaviour of thyroid cancer has been noticed (31). The explanation of this increased aggressiveness is not well known but it has been suggested that thyroid stimulating antibodies (TSAb) may be responsible (30). The small number of patients presenting with such association in our series does not allow us to draw any significant conclusion about the aggressiveness of thyroid carcinoma and hence about the need of a more

aggressive surgical treatment. However, no signs of metastases or extrathyroid invasion were observed in the two patients presenting with such association and they are still alive without evidence of malignancy after 15 months and 19 years, respectively.

It has been reported that the association between thyroid carcinoma and Graves' disease seems to be more frequent when a palpable cold nodule is present. In this case the risk of malignancy has been calculated to be very high (45.8 per cent) (30). This result has been confirmed also by another study in which the incidence of thyroid carcinoma in Graves' patients with a palpable cold thyroid nodule resulted much higher (22.2 per cent) compared to that observed in patients without a recognisable thyroid nodule (2.9 per cent) (15). It should be noted that palpable nodules have been observed in a relevant proportion of Graves' disease patients (15,8 per cent) and this value has been calculated to represent at least two-fold the frequency expected in the general population during the same period (4). In our population of 38 patients with toxic diffuse goiter that underwent thyroid surgery only one had a palpable cold nodule that proved to be malignant at the final histologic examination. This observation suggests that every cold area in a diffusely enlarged and hyperfunctioning thyroid gland should be carefully evaluated because it is at high risk of harbouring malignancy.

In conclusion, thyroid carcinoma in patients with hyperthyroidism should not be considered a rare finding and malignancy should be always ruled out, particularly in patients with palpable cold nodules in the contest of a diffuse toxic goiter as well as in patients with toxic adenomas which appear to show higher rates of concurrence of the two thyroid diseases.

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