Papillary Carcinoma of the Thyroid in an Autonomously Functioning Nodule

apresentação de casos

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ABSTRACT

The association of differentiated thyroid cancer and a functioning nodule is very low. We report on a case of papillary carcinoma in an autonomously functioning thyroid nodule in a 39 year-old female patient. The nodule extended to the whole right lobe and ^{131}I scintigraphy has detected a "hot" nodule and a partial suppression of ^{131}I uptake in the left lobe. Serum TSH levels (RIA) were undetectable (<1.0µUI/mL), but total T3 (190ng/dL) and T4 (8.5µg/dL) were normal. The patient underwent a partial thyroidectomy and an adenomatous nodule was found with a small central nucleus (7mm) hosting a papillary carcinoma. Whole body scans detected only residual thyroid uptake and the patient was subsequently treated with 100mCi of ^{131}I. The patient has been on replacement therapy with 150µg of L-thyroxine and free of tumor recurrence for 12 years after surgery. In conclusion: the present report confirms other published cases in which the presence of a "hot" thyroid nodule does not exclude the concomitance of a well-differentiated thyroid carcinoma. **(Arq Bras Endocrinol Metab 2003;47/6:739-743)**

Keywords: Carcinoma; Papillary; Graves' disease; Hot nodule; Thyroid carcinoma; Thyroid nodule

RESUMO

Carcinoma Papilar da Tiróide em Nódulo Funcionante Autônomo.
A associação de câncer diferenciado da tiróide com nódulo funcionante é muito baixa. Apresentamos uma mulher de 39 anos com carcinoma papilar em nódulo autônomo funcionante da tiróide. O nódulo ocupava todo o lobo direito e o estudo cintilográfico com I^{131} detectou um nódulo quente e supressão parcial da captação de I^{131} pelo lobo esquerdo. Os níveis de TSH (RIE) eram indetectáveis (<1,0µUI/mL), mas os de T3 (190ng/dl) e T4 total (8,5µg/dl) normais. Submetida à tiroidectomia parcial, encontrou-se nódulo adenomatoso com um pequeno núcleo central (7mm) com carcinoma papilar. A pesquisa de corpo inteiro mostrou somente captação residual da tiróide e a paciente foi tratada com uma dose de 100mCi de I^{131}. A paciente está recebendo terapia substitutiva com 150µg de L-tiroxina e 12 anos após a cirurgia não apresenta qualquer sinal de recorrência tumoral. Em conclusão: a paciente descrita confirma outros casos publicados de que a presença de um nódulo "quente" da tiróide não exclui a possibilidade da ocorrência de um carcinoma bem diferenciado. **(Arq Bras Endocrinol Metab 2003;47/6:739-743)**

Descritores: Carcinoma papilar; Doença de Graves; Nódulo quente; Carcinoma da tiróide; Nódulo da tiróide

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THE ASSOCIATION OF THYROID carcinoma and hyperthyroidism is presently considered more frequent than it was in the past (1). The most frequent association of thyroid carcinoma is with "hot" nodules, with

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or without manifestations of hyperthyroidism (2-5), whereas the association with Graves' disease is considered to be rare (6,7).

The majority of thyroid carcinomas associated with hyperthyroidism or with a hyperfunctioning nodule is of the papillary type, followed by follicular carcinoma (2-5,8); less frequently, Hürtle cell (5), anaplastic (8), and medullary carcinoma (9) have also been described.

The diagnosis of thyroid cancer before surgery through biopsy and cytology is not frequent (4), due to the following: a) the association of thyroid cancer and hyperthyroidism is considered to be very rare; b) thyroid carcinoma originates inside the hyperfunctioning nodule, but it can be located someplace else in the gland (1,6,9). The belief that hyperthyroidism or hyperfunctioning nodule would dismiss the possibility of thyroid cancer, and the fact that a thyroid carcinoma can occur just or near the hyperfunctioning nodule, or someplace else in the gland (1), are what makes the pre-surgical diagnosis by biopsy and cytology less frequent (4).

Herein we report the case of a woman with a papillary thyroid carcinoma presenting in an autonomously hyperfunctioning nodule, an uncommon combination until 1990, when only 17 cases of this association were reported (1). However, in the past 12 years several other cases have been published (3,4,6,7,10-12).

CASE REPORT

A 39 year-old white woman was referred for obesity treatment in 1988. She was nullipara, with regular menses, and had no clinical evidence of hyperthyroidism. Although the patient was from an endemic goitrous area, there was no record of thyroid diseases in her family history. She did not have a record of radiotherapy on her neck area. Her height and weight were 152cm and 74.5kg (BMI: 31.1). On physical examination, a large nodule was palpable in the right thyroid lobe.

^{131}I-scintigraphy demonstrated an area of high iodine uptake occupying all right lobe, with reduced uptake in the left lobe (figure 1). After a T3 suppression test (75µg daily for 8 days), the thyroid scintigram remained unchanged: basal and post-suppressive thyroid ^{131}I-uptakes were 47.8% and 32.7%, respectively. T3 (190ng/dL; NR: 80-210ng/dL) and T4 (8.5µg/dL; NR: 4.5-12µg/dL) were normal by IRMA, but TSH levels were undetectable (<1.0µUI/mL), as were thyroglobulin and microsomal antibodies. Routine laboratory data were unremarkable. The patient was diagnosed with a sub-clinical autonomous functioning thyroid nodule and observation was recommended.

Three years later the nodule had increased significantly, extending to the entire right lobe. ^{131}I-scintigraphy demonstrated the same large hyperfunctioning area. Two ultrasound (US)-guided fine needle biopsy aspirations (FNBA) disclosed follicular cells without atypia, and a thyroid surgery was performed. The right thyroid lobe weighed 15g and measured 4.5 x 4.5 x 2.5cm. On cutting section a 0.7cm white nodule of increased elastic consistence was observed; histological examination revealed an adenomatous nodule with a small papillary carcinoma focus (7mm) (figure 2) and vessel invasion. Total thyroidectomy was then performed and the rest of the gland was histologically normal.

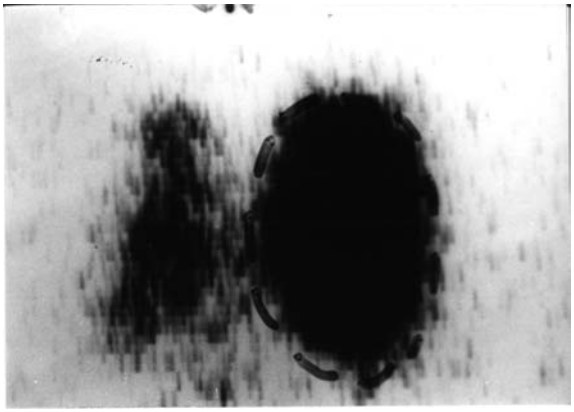

Figure 1. Thyroid ^{131}I-scintigram shows a "hot" nodule in the right lobe and decreased ^{131}I-uptake in the left lobe.

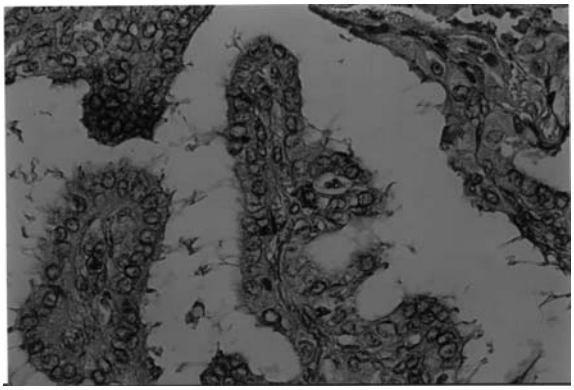

Figure 2. Histological section of papillary thyroid carcinoma. Papillary projections show disposed cells along conjunctive-vascular axes. Nuclei are clear or in dull-glass, with rifts in the nuclear membranes (40X; hematoxylin-eosin staining).

Because a subsequent ^{131}I whole-body scan showed some uptake in the cervical area, a 100mCi dose of ^{131}I was administered. The patient was thereafter maintained on suppressive L-thyroxine therapy with daily doses of 150µg. On follow-up TSH (<0.05µUI/mL) and thyroglobulin (0.5ng/ml; NR: <38.2) were kept suppressed. Subsequent ^{131}I-whole body scans were consistently negative.

One-year later, conjunctival hyperemia and mild bilateral exophthalmia were observed. Orbital computerized tomography disclosed increased density of the retro-orbital fat, mainly in the right side, with a small thickening of the retro-lateral muscle. The patient has been in good health and free of symptoms for the past 12 years.

DISCUSSION

The association of autonomous nodular goiter and differentiated thyroid carcinoma seems more frequent than it was supposed, having been increasingly reported lately in surgical series: 3.1% (8), 6% (2), 16% (3), 17.8% (5), and 17.9% (13). In children this association is described in 11.3% of the cases (14).

A carcinoma associated with hyperthyroidism is rarely diagnosed before surgery (4) and this is largely due to the fact that the majority of the patients had an occult microcarcinoma defined as a tumor with less than 1cm (5). Fine-needle aspiration biopsy (FNAB) coupled with cytological examination is the most effective procedure for the diagnosis of thyroid cancer (15). However, this method is limited when small amount of cells is obtained. The diagnosis of occult thyroid carcinoma was missed in our patient after two FNAB.

Another problem in diagnosing cancer associated to hyperfunctioning nodules by FNAB is that it may not reside inside the adenoma, as in the present case, but can also be someplace else in the gland (1,13). For instance, hyperthyroidism and thyroid carcinoma were two separate illnesses in 45% of patients (13). Thus, it is important to perform US-guided FNAB to increase the chances of diagnosing a thyroid cancer, including occult ones with <1cm that could reside in different areas of the gland (15).

As in the present case, hyperthyroidism is most commonly associated with a papillary cancer (2-5,8), and the cytological diagnosis is straightforward provided enough material is obtained by FNAB (15). However, in a few patients the cytological diagnosis of follicular cancer is challenging, since capsular or blood vessel invasion, as required for diagnosis, may not be evident.

Hyperfunctioning thyroid nodule is a benign condition that progress slowly to symptomatic hyperthyroidism, since most patients are diagnosed after 50 years of age (16). The most common association of hyperfunctioning nodules is papillary cancer (2-5,8), and age (>50 years) seems to be one of the most important prognostic factors in papillary cancer (16). Usually, a careful observation through periodic evaluations is indicated for the asymptomatic or sub-clinical forms (16). When clinical hyperthyroidism takes place or TSH becomes suppressed, surgery or radioiodine therapy is indicated; recently, percutaneous intranodular ethanol injections have been also used (17-19).

Our patient was initially treated with a partial thyroidectomy, due to a large hyperfunctioning right lobe nodule. This type of treatment is effective in providing immediate relief of symptoms (3,16,19,20). Later, when the presence of an occult carcinoma inside the thyroid nodule was verified, total thyroidectomy complemented by ablative ^{131}I-therapy (100mCi) was carried out. Some investigators recommend that occult thyroid carcinomas (<10mm in diameter, as in our patient), should be treated by lobectomy plus T4 suppressive therapy (8,21); they contend that the prevalence of an occult thyroid carcinoma in a normal population is 5-10%, whereas the prevalence of clinically evident thyroid cancer is only 0.05%; thus, during a lifespan only 1-2% of occult carcinomas may progress to an overt tumor (21). On the other hand, Furlan et al. (22) demonstrated similar incidences of metastatic nodal disease, distant metastases, recurrent neck metastatic disease, and multicentricity in bearers of occult thyroid cancer and obvious thyroid carcinoma. These authors thereby indicate near-total thyroidectomy and plus radioiodine ablation, as done in our patient. Besides, the blood vessel invasion seen in our patient's occult carcinoma is an unfavorable histological feature.

Radioiodine therapy for the hyperfunctioning nodule may fail in improving thyroid function (3), and may be associated with a high incidence of hypothyroidism (16). Radiation doses higher than those used to treat Graves' disease may be necessary, due to the greater resistance of adenomas (16). However, ^{131}I-therapy seems as effective in treating well-differentiated metastatic thyroid cancer (23), as in treating occult thyroid carcinoma associated with a hyperfunctioning nodule, as in the present case.

Percutaneous intranodular ethanol injection (PIEI) is an effective treatment for the hyperfunctioning thyroid nodule (18). The initial experience with PIEI (17) was based on the previous observation that intratumoral ethanol was effective in treating the small

hepatocellular carcinoma (24). It is also possible that PIEI could destroy the differentiated carcinoma inside the hyperfunctioning nodule. We are not aware of any patient bearing a hyperfunctioning nodule and treated with PIEI who has developed metastases of an occult carcinoma in the long run. Recently, it has been shown in patients with papillary thyroid carcinoma with metastases limited to cervical nodes that PIEI was successful in the long-term control of metastatic adenopathy (25). This observation justifies the use of PIEI to treat a hyperfunctioning thyroid nodule harboring an occult thyroid carcinoma (as in our case) without the need of a prior biopsy and / or surgery.

Finally, we could not rule out the possibility that our patient had Graves' disease. She had an elevated and only slightly T3-suppressive ^{131}I-uptake. On follow-up a moderate mostly unilateral exophthalmia occurred and findings of an orbital CT were suggestive of Graves' disease. The concurrence of toxic adenoma and Graves' disease is rare (6,7). In addition, the possible association of thyroid carcinoma and Graves' disease would have made this case even more unusual, since only a few cases have been reported to date (3,4,7,26-29). In a series of 202 patients with hyperthyroidism who underwent thyroidectomy, thyroid cancer was diagnosed in 5.3% of patients with Graves' disease (5). In another series of 273 patients with thyroid carcinoma, 1.5% had Graves' disease (13).

In conclusion, the present report confirms other published cases in whom the presence of a "hot" nodule on thyroid scintigraphy does not exclude the possible concomitance of a well-differentiated thyroid carcinoma.

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