Hyperfunctioning thyroid cancer: a five-year follow-up

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SUMMARY

Differentiated thyroid cancer rarely occurs in association with hyperfunctioning nodules. We describe a case of a 47-year-old woman who developed symptoms of hyperthyroidism associated with a palpable thyroid nodule. Thyroid scintigraphy showed an autonomous nodule, and fine-needle aspiration biopsy was suggestive of papillary carcinoma. Laboratorial findings were consistent with the diagnosis of hyperthyroidism. The patient underwent thyroidectomy and a papillary carcinoma of 3.0 x 3.0 x 2.0 cm, follicular variant, was described by histological examination. The surrounding thyroid tissue was normal. Postoperatively, the patient received 100 mCi of ¹³¹I, and whole body scans detected only residual uptake. No evidence of metastasis was detected during five years of follow-up. Hot thyroid nodules rarely harbor malignancies, and this case illustrated that, when a carcinoma occurs the prognosis seems to be very good with no evidence of metastatic dissemination during a long-term follow-up.

CASE REPORT

A 47-year-old woman was referred to us in May 2003, because of a thyroid nodule and hyperthyroidism. She complained of weight loss (not quantified), nervousness, tremor, fatigue and insomnia, which had begun three months earlier. Also, she had been noting a slow and progressive increase in the anterior neck region during the last two years. Her menses were regular, and...
there was a positive family history for non-neoplastic thyroid disease. There was no history of previous radiation on her cervical region. On physical examination, she weighed 54 kg and was 160 cm tall (body mass index, BMI, 21.09). Her resting pulse rate was 94 beats/min, and her blood pressure was 140 x 90 mmHg. On thyroid topography, an approximately 2.5 cm, mobile, painless nodule was palpable on the right side. No lymph nodes were detectable on examination of the neck.

Ultrasonographic study showed a solid nodule of 2.6 cm diameter in the right thyroid lobe, with the rest of the gland echographically normal. Scintigraphy with 131I showed the presence of an area of high iodine uptake occupying the right lobe of the thyroid, corresponding to a hyperfunctioning nodule, and no uptake was detected in the remaining bed (Figure 1A). Radioiodine uptake of the neck region was 32% after 24 hours (normal range, 10%-45%). Free T4 serum levels were 2.75 ng/dL (normal range, 0.7-1.5 ng/dL), total T3 was 3.53 ng/mL (normal range, 0.7-2.2 ng/mL) and TSH was less than 0.05 mUI/mL (normal range, 0.3-5.0 mUI/mL). On the basis of these findings, a diagnosis of an autonomously functioning thyroid nodule was made.

The patient was also submitted to a fine-needle aspiration biopsy of the nodule that was suggestive of a papillary carcinoma (Figure 1B). Methimazole therapy was initiated (40 mg/day) and after two months the patient was in euthyroidism. In August 2003, total thyroidectomy was performed and the postoperative course presented no complications.

Histological examination confirmed that the nodule, measuring 3.0 x 3.0 x 2.0 cm was a papillary carcinoma, follicular variant, with capsular and vascular invasion (Figure 1C). The tumor was not multicentric, and the rest of the thyroid gland was histologically normal.

Two months after surgery the patient was in frank hypothyroidism and a 100 mCi 131I dose was administered. 131I whole-body scan showed only some uptake in the cervical area. Subsequently, levothyroxine was instituted in a dose of 150 µg per day to suppress the TSH production by the pituitary gland. One year after surgery a 131I whole-body scan was performed and again only residual uptake in the cervical area was observed. Thyroglobulin levels measured on hypothyroidism, were undetectable and antithyroglobulin antibodies were negative. The patient was maintained on levothyroxine suppressive therapy and three years after surgery cervical ultrasonography showed a heterogeneous oval nodule with internal calcifications, measuring 7 x 12 mm, localized on thyroid topography. Fine needle aspiration biopsy was negative for malignancy and thyroglobulin measured in the aspirate washout was 0.2 ng/dL. At that time, thyroglobulin serum levels were 0.4 ng/mL, serum antibodies were negative and no intervention was performed. The dose of levothyroxine was reduced to 125 µg/day and no evidence of recurrence of the disease was observed during the next two years of follow-up, once thyroglobulin and antithyroglobulin antibodies were undetectable in the patient serum.

**DISCUSSION**

The hyperfunctioning thyroid nodule has been generally considered a benign disease requiring a conservative therapeutic approach and in the past it was believed that hyperthyroidism excluded the possibility of a thyroid carcinoma. However, in the last years, there has been citation of cases of thyroid cancer associated with solitary toxic goiter, multinodular toxic goiter, diffuse toxic goiter (Graves’ disease) and hyperfunctioning thyroid metastases (3,7-12).

We described here the case of a hyperthyroid woman who had a diagnostic suspicion of thyroid carcinoma in a fine-needle aspiration biopsy which is a very uncommon feature. The literature reports a crescent number of cases of hyperthyroidism associated with thyroid microcarcinomas diagnosticated after histopathological examination, while malignant tumors of more than 1.5 cm diameter, which are proved to be autonomous, are very rare. The most frequent histological type of cancer in these cases seems to be the papillary (70% to 75%), followed by the follicular type (20% to 25%). Medullary and anaplastic forms are rarely observed (7).

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**Figure 1.** (A) Thyroid 131I-Scintigraphy shows a hyperfunctioning nodule in the right lobe; (B) aspirate smears show follicular clusters of cells with large and pale nuclei, and rare intranuclear inclusions; (C) histologic sections revealed a papillary carcinoma, follicular variant.
In a five-year follow-up, our patient presented no evidence of metastases. The age at diagnosis, sex, histopathologic type (a papillary carcinoma), and low diameter of the tumor (less than 4 cm) were probably distinguished characteristics that contributed to the good outcome in this period. In the previous analysis of 19 patients followed-up for a median duration of 6 years, frequency of locoregional and distant metastases did not differ from differentiated thyroid carcinomas in general (4). The survival prognosis was close to that of matched follicular subtypes of differentiated thyroid cancer (4). In the same study, 4 out of 19 patients harbored a papillary carcinoma and 2 of them were follicular variants. The first was a 56-year-old man who presented a carcinoma T2N0M0 at the initial stage with no evidence of distant metastases during 17 years of follow-up. The second patient was also a man, who had the diagnosis at the age of 74 and the tumor was a T4N0M0. He presented distant metastases during follow-up, and after six years he was still alive (4). The etiopathogenesis of coexisting hyperthyroidism and carcinoma is still unknown. Concerning autonomous thyroid adenomas, mutations in the TSH receptor gene (TSHR) and in the Gsα protein gene (GNAS1) have been identified to be the cause of the majority of the cases (13,14). Also, in hyperfunctioning carcinomas mutations in the TSH receptor gene have been described (6,15-17). However, from the data available in the literature, it seems that activation of the cAMP pathway is not a major player in cell transformation. Most hyperfunctioning tumors harbor both TSHR mutations and proto-oncogene mutations. This coexistence suggests that carcinomas arise from the activity of classical oncogenes such as RAS and RET/PTC, and that the TSHR and GNAS1 mutations confer hyperfunctioning features to the neoplasms (18). In the present study, we did not investigate the possibility of mutations that could be related to the pathogenesis of the disease.

Considering the rarity of the association of thyroid cancer and hyperthyroidism, at present, the evidences available are not enough to recommend the systematic evaluation of oncological risk in all hot thyroid nodes, which may be cumbersome and not necessarily cost-effective. Further studies would be helpful to clarify this issue.

In conclusion, the present report illustrates that hyperthyroidism does not exclude thyroid malignancy and confirms other published cases in which the prognosis of the carcinoma seems to be very good, with elevated survival rates, especially in the papillary histological subtype.

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REFERENCES