

Case Reports

Functioning Thyroid Carcinoma Occurring in Graves' Disease: A Report of one Case and Review of the Literature

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Most of the previous reports of thyroid carcinoma associated with thyrotoxicosis have been described in patients with toxic adenoma¹⁻⁴ or with functioning extensive bony or pulmonary metastases.⁵⁻⁷ The occurrence of carcinoma in Graves' disease is rare. Most of the reported cases were due to coexistent hypofunctioning (cold) nodules.⁸⁻¹⁰ Carcinoma in functioning (warm or hot) nodules in association with Graves' disease is extremely rare. Reviewing the literature, we found one similar case of functioning malignant thyroid nodule coexistent with Graves' disease.¹¹

We report a female patient who had thyroid carcinoma arising in a diffuse toxic goiter. She presented with typical clinical and biochemical features of Graves' disease. Tc-99m scintigraphy of the thyroid showed diffusely increased uptake with functioning (warm) nodule. Histopathologic examination of the resected thyroid proved the warm nodule to harbor papillary carcinoma. Serum thyrotropin-binding inhibiting immunoglobulin (TBII) was positive in high concentration.

The incidence of thyroid carcinoma in Graves' disease and the possible carcinogenic role of thyroid immunoglobulins is discussed.

Case Report

A 45-year-old female presented with a history of anterior neck swelling of four months' duration. She complained of nervousness and irritability with trembling of the hands and passing of loose stools. She lost 8 kg in weight during this period. There was no past history of radiation therapy to the head or neck.

Physical examination revealed a remarkably anxious patient with a staring look and fine tremors of the outstretched hands. The left thyroid lobe was diffusely enlarged with a palpable nodule approximately 1.5 cm in

diameter felt in the lower pole. Pulse rate was 120/min and regular and blood pressure was 140/50 mm/Hg. Heart, chest and abdominal examinations were noncontributory.

Chest x-ray, ECG, BUN, glucose and electrolytes were all normal. Serum free T4 was 40.2 pmol/L (normal range 11.5 to 32.0), free T3 14.1 pmol/L (normal 2.5 to 7.7) and TSH less than 1.0 μ U/mL (normal is less than 5.0). Microsomal and thyroglobulin antibodies as well as TBII were present in high concentrations in the serum.

Twenty-four hour radioactive iodine uptake (RAIU) was 38% (normal 10% to 30%). Thyroid scan with Tc-99m showed an enlarged thyroid gland with diffuse uptake mainly in the left lobe and a localized area of condensed tracer uptake in the lower pole, indicating a functioning (warm) nodule (Figure 1).

She underwent uneventful surgery after achieving a euthyroid state with carbimazole. Intraoperative findings were enlarged thyroid lobes, a solid grayish nodule measuring 1.5 x 1.0 cm in the lower pole of the left lobe and two enlarged lymph nodes along the left inferior thyroid veins. A left total and right subtotal lobectomy were performed. The two enlarged lymph nodes were resected.

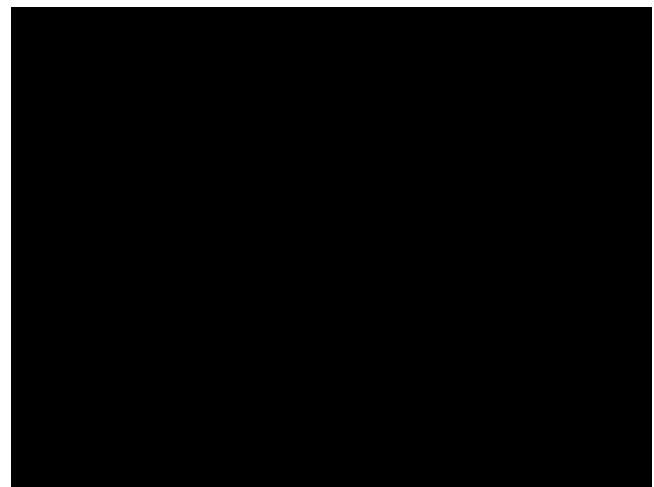


FIGURE 1. Radioisotope scan with Tc-99m showing enlarged thyroid gland with diffuse uptake and a functioning (warm) nodule in the lower part of the left lobe.

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FIGURE 2. Histopathologic section of the thyroid nodule showing irregular and variable size follicles lined by epithelial cells which show papillary infoldings. (H&E 200x.)

Macroscopic examination of the resected specimen showed the left lobe measuring 5.0 x 4.0 x 8.0 cm. The cut surface showed a 1.5 x 1.0 x 1.0 cm grayish firm nodule. The right lobe measured 4.0 x 3.0 x 5.0 cm with a homogeneous cut surface. Microscopically (Figure 2), the follicles were irregular and variable in size with very scanty colloid and peripheral vacuolation. The follicular epithelium showed mitotic figures and papillary infoldings with nuclear chromatin abnormalities in many areas. In a small area in one section from the left lobe, there was a cancerous proliferation of the glandular epithelium with a characteristic pattern of papillary carcinoma (WHO classification of tumors, 1974). Several other sections of both lobes revealed no evidence of cancer invasion but showed features of treated primary thyroid hyperplasia. One lymph node showed metastatic deposits of papillary carcinoma.

Two weeks after surgery, the patient was given an ablative dose of I¹³¹ and maintained thereafter on thyroxine 200 µg/day. She remained well with no evidence of recurrence during follow-up over the next six years.

Discussion

Much controversy surrounds the incidence of thyroid cancer in association with Graves' disease. It was thought that patients with hyperthyroidism have a lower incidence of thyroid cancer than euthyroid patients.¹²⁻¹⁴ Subsequent reports challenging this view have shown a rising incidence of this association.^{10,15,16}

Earlier reports estimated the incidence of thyroid carcinoma in autopsy series of clinically normal thyroids to range between 0.1% to 0.2%,^{9,17} while others have reported an incidence of occult papillary carcinoma in autopsy specimens in Japan and Hawaii ranging from 13% to 24%.^{18,19} In 1951, Behrs et al.²⁰ reported 14 cases of

thyroid carcinoma in 3022 cases of Graves' disease, an incidence of 0.5%. In 1954, Sokal⁸ reviewed 10,839 patients with Graves' disease and found seven cases (0.06%) of thyroid carcinoma. Dobyns et al.¹² conducted a multicenter prospective study involving 10,013 patients with Graves' disease treated surgically and found a cancer incidence of 0.4%. Later on, Behar et al.¹⁰ reported an incidence of 5.2% and Farbota et al.¹⁵ 5.1% of thyroid cancer in their series of patients treated surgically for Graves' disease. More recently, Reiger et al.²¹ reported 0.76% and Fong et al.²² 1.5% incidence rates of thyroid carcinoma in their series of Graves' patients treated surgically. This wide variation of incidence rates may in part be due to racial and geographical variations or possibly due to improved techniques in pathologic examination in some studies.

The occurrence of carcinoma in functioning (warm or hot) nodules in association with Graves' disease is extremely rare. Reviewing the literature, we found only one similar case of functioning malignant thyroid nodule in association with Graves' disease in the series reported by Edmonds et al.¹¹

The usual scintigraphic finding in thyroid carcinoma is a hypofunctioning (cold) nodule. In spite of the appearance of a functioning (warm) nodule on scintigraphy in our patient, this nodule harbored malignancy. This might be explained by a dissociation between anion trapping and organification of iodine, which may be seen in a small fraction of thyroid malignancies and therefore appear hyperfunctioning by Tc-99m but hypofunctioning by iodine imaging.²³

The fact that carcinoma was not suspected clinically in this case is not surprising. In a review of 138 thyrotoxic patients reported by Terzioglu et al.,²⁴ thyroid carcinoma was found in eight patients. None of the patients was suspected of having carcinoma before or during operation.

The exact relationship of thyroid carcinoma to Graves' disease is unclear. The prevailing hypothesis of thyroid carcinogenesis is that TSH constitutes the single most important factor in promoting growth and possibly the genesis of thyroid carcinoma.^{10,15} Animal studies had clearly shown the role of chronic stimulation of the thyroid by TSH and goitrogenic diets in promoting thyroid hyperplasia and later neoplasia.^{16,17,25} In spite of this, there is no acceptable evidence of malignancy in dys-hormonogenetic goiters where there are high and sustained TSH levels.²⁶

However, TSH is suppressed in Graves' disease, so the stimulation of thyroid is not through TSH, but probably through circulating thyroid stimulating antibodies (TSAB).²⁷ Some workers have raised the role of long acting thyroid stimulator (LATS) and LATS-protector (LATSP) in stimulation of carcinogenesis in Graves' disease.^{28,29} More recently, increasing reports on the

possible carcinogenic role of TBII and other immunoglobulins in Graves' disease are seen in the literature.^{11,15,30}

All these findings suggest the possible carcinogenic role of Graves' immunoglobulins interacting with TSH-receptors producing thyroid hyperplasia and later neoplasia. Some recent reports showed that Graves' disease and Graves' immunoglobulins not only influence the development and genesis of thyroid carcinoma, but also affect the behavior of these tumors as they grow larger and behave more aggressively than those associated with autonomous thyroid nodules.³⁰⁻³² Other workers have suggested that these clinically silent cancers may represent dormant tumors ready to become clinically apparent with appropriate stimulation as, for example, by TSH or by TSAB in hyperthyroidism.¹⁸ Finally, the influence of these immunoglobulins in genesis of thyroid malignancy remains speculative and further work is required to substantiate and delineate the role of these immunoglobulins in thyroid carcinogenesis.

In conclusion, such cases emphasize the importance of careful search for malignancy in apparently benign looking functioning nodules and the presence of a hyperthyroid state should not rule out the possibility of an associated thyroid malignancy.

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