An Autonomously Functioning Thyroid Carcinoma Associated with Euthyroid Graves' Disease

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A 39-yr-old man with an autonomously functioning thyroid carcinoma is presented. Only 17 similar cases have been reported in the literature. The patient had unilateral Graves' ophthalmopathy. He was euthyroid as reflected by normal TSH concentration, whereas the results of a T_3 suppression test established the presence of autonomous thyroid function. A thyroid scan with ^{123}I revealed a hot nodule corresponding to the location of a papillary carcinoma and remained substantially unchanged after T_3 administration. The hyperfunction of the carcinoma itself was clearly confirmed by the intense concentration of ^{131}I within the tumor on microautoradiograms. While a hot nodule on radioiodine scan is unlikely to be malignant, the possibility of carcinoma should not be overlooked.

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Autonomously functioning thyroid carcinoma is considered to be extremely rare, with only 17 such cases reported in the literature (*1–11*). Three of the reported cases were euthyroid (*2–4*), and the remainder were hyperthyroid (*1,2,5–11*). None of these cases had ophthalmopathy typical of Graves' disease. In this report, we present a case of a carcinoma associated with euthyroid Graves' disease. Laboratory, autoradiographic and histological findings are described.

CASE REPORT

A 39-yr-old Japanese man noticed gradual development of left painless proptosis in September 1990. The patient was referred to our department in December 1990. He had no symptoms suggestive of hyperthyroidism. On physical examination, a hard nodule with ill-defined margins was palpable in the mid-portion of the right thyroid lobe. No bruit was heard. There was no cervical node enlargement. Left proptosis with retraction of the upper eyelid was observed, and, on exophthalmic measurements, the left was 25 mm and the right was 18 mm. Routine laboratory data showed no abnormality. Thyroid hormone assays were normal: free T_3 (RIA) 3.49 pg/ml (normal 2.25–5.36); T_3 (RIA) 91.3 ng/ml (normal 80–190); free T_4 (RIA) 0.94 ng/dl (normal 0.7–2.1); T_4 (EIA) 6.2 μg/dl (normal 4.6–11.0); TSH (EIA) 0.38 μU/ml (normal 0.27–6.00). Furthermore, TSH response to 500 μg TRH injection was normal (TSH max. was 13.22 μU/ml at 30 min). TSH receptor antibody (TRAb) measured using Smith's kit was slightly elevated (an inhibition rate of 13%, normal −10% to +10%). Thyroglobulin (Tg) antibody was negative and Tg (RIA) was increased (91.7 ng/ml, normal <30). A thyroid uptake test and scintigraphy with 3.7 MBq of ^{123}I were performed. The radioiodine uptake was 10.7% at 3 hr and 23.4% at 24 hr. The scintigram demonstrated an area of "hot" accumulation in the right lobe, while the rest of the gland showed decreased activity (Fig. 1A). After subsequent suppression with triiodothyronine (75 μg daily for 8 days) radioiodine uptake was slightly decreased to 8.5% at 3 hr and 19.2% at 24 hr. The thyroid scintigram remained substantially unchanged after T_3 administration (Fig. 1B). Remarkably, the rest of the gland failed to respond to T_3 suppression. On thyroid ultrasonogram, a hypoechoic mass with ill-defined margins was observed in the mid-portion of the right lobe. Bright echoes with acoustic shadows indicating the presence of calcification were scattered within the mass. Both plain radiography and computed tomography, however, failed to show any calcification in the gland. A histological specimen obtained by ultrasound guided large needle biopsy of the nodule revealed a papillary carcinoma, but fine needle aspiration cytology failed to disclose malignancy. Orbital magnetic resonance imaging (MRI) showed enlargement of the left eye muscles without the swelling of their tendons. Orbital tumors were not found. These characteristic MRI appearances and clinical features, such as a painless, gradual onset and presence of upper eyelid retraction, led to a diagnosis of Graves' ophthalmopathy.

Subtotal thyroidectomy with right modified radical neck dissection was performed in January 1991. A tumor mass measuring 1.5 × 1.0 cm was found in the resected thyroid gland. Histologically, the tumor was composed of papillary growth of follicular cells with ground-glass nuclei (Fig. 2). Many psammoma bodies were scattered within the tumor. The rest of the gland revealed somewhat hyperplastic changes of follicles. Metastatic carcinoma was microscopically observed in 9 of 22 excised cervical nodes. Graves' ophthalmopathy was treated with intravenous methyl-

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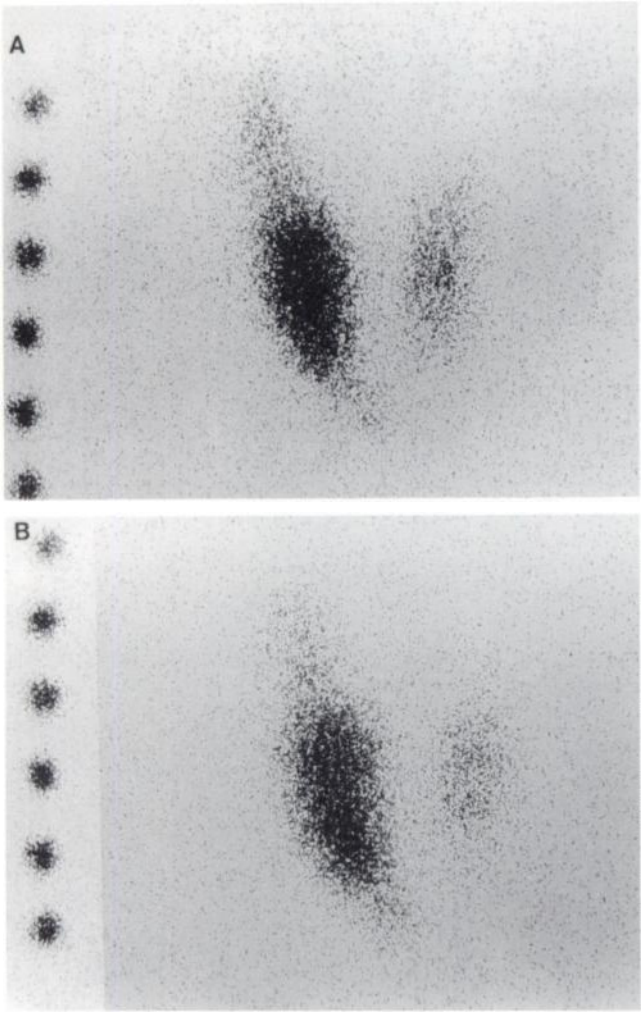

FIGURE 1. (A) Thyroid scintigram with ^{123}I demonstrates a hot nodule in the right lobe. The rest of the gland shows less radioactivity. The distance between the two point sources is 2 cm. (B) Thyroid scintigram after administration of T_3 reveals the same findings as (A).

prednisolone and showed a clear response. Orbital MRI revealed a pronounced reduction in the bulk of the left eye muscles.

Twenty-four hours prior to the surgical operation, 74 MBq of ^{131}I was administered to evaluate the localization of radioiodine in the thyroid gland. Microautoradiograms revealed significant ^{131}I accumulation in the carcinomatous area as well as in the surrounding thyroid parenchyma (Fig. 3). The degree of the ^{131}I concentration was greater in the former than in the latter.

DISCUSSION

The coexistence of thyroid carcinoma and hyperthyroidism is currently considered to be incidental, and is thought to result from the following conditions (*1,5*): (a) thyroid carcinoma, which is imaged as a cold nodule on radioiodine scintigram, within a diffuse or multi-nodular toxic goiter; (b) carcinoma as a cold nodule either adjacent to or within an autonomously hyperfunctioning adenoma; (c) hyperfunctioning carcinoma itself showing a hot nodule.

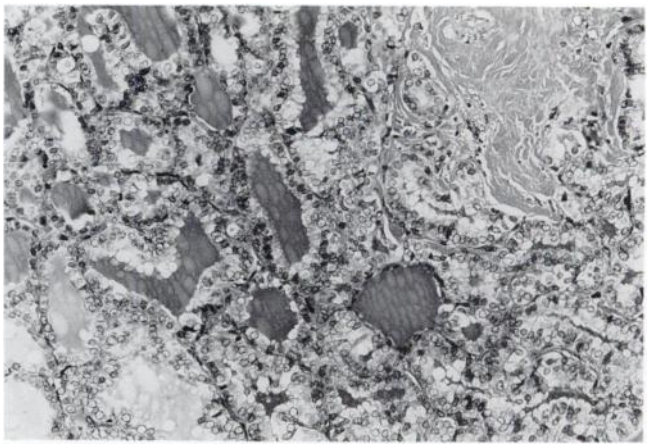

FIGURE 2. Papillary carcinoma characterized by dense proliferation of follicular cells with ground-glass nuclei.

Hyperthyroidism attributed to thyroid cancer has been rarely described. In 1946, Leiter et al. first reported two cases of thyroid cancer with hyperthyroidism due to functioning metastases (*12*). Thereafter, approximately 32 such cases have been reported (*6,13–18*). In some of these cases, hyperthyroidism was documented prior to thyroid surgery. On the other hand, in the majority hyperthyroidism developed after complete thyroidectomy due to voluminous functioning metastatic lesions.

According to a careful analysis of the literature by Rosa et al. in 1990 (*1*), 17 cases of autonomously functioning thyroid carcinoma without functioning metastases have been reported in the past 25 years (*1–11*), with the present case constituting an additional one of this category. Fourteen of these patients manifested hyperthyroidism (*1,5–11*), and four patients, including our patient, were euthyroid (*2–4*). Sixteen patients were female and two were male. In 13 patients, the carcinoma was a papillary type, and in the remaining five patients it was follicular. All of the patients except the one discussed here came to medical attention because of hyperthyroidism and/or a thyroid

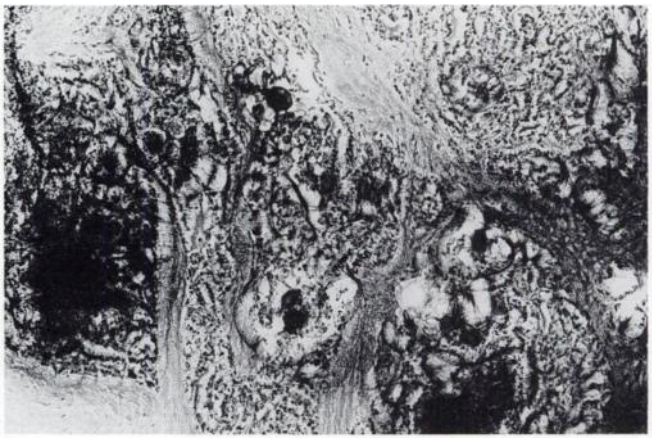

FIGURE 3. Microautoradiogram demonstrates intense ^{131}I accumulation both in the carcinoma and in the surrounding thyroid parenchyma.

tumor. Only in our patient was Graves' eye disease the dominant clinical feature.

The identification of a hot nodule and a thyroid cancer in the same area does not always indicate the presence of a functioning thyroid carcinoma. The concurrent presence of a "cold" carcinoma within a "hot" adenoma may represent a hot nodule (*19,20*). A "cold" carcinoma may be shown as a hot nodule when the thickness of the surrounding thyroid parenchyma is focally increased. Therefore, to lead to a diagnosis of a "hot" thyroid carcinoma, it is essential to verify the presence of the hyperfunction of the cancer itself, which can be recognized on autoradiograms. In our patient, the location of a papillary thyroid cancer corresponded to the area of increased uptake on the scan, and ^{131}I accumulation in the carcinoma, which was greater than that in the surrounding parenchyma, was verified on microautoradiograms. In addition, evidence for the hyperfunction of the carcinoma was found in immunohistochemical and electron microscopic examinations (data not shown), intense immunohistochemical staining for Tg, T_4 and T_3 and ultrastructural finding of a well-developed rough endoplasmic reticulum (rER) in the carcinoma cells.

In a hot nodule, the size of the area of increased uptake on the scan looks larger than its real size, and depends on its amount of radioactivity rather than its actual size. In our patient, the hot area on the scan reflects not only the concentration of radioiodine in the "hot" carcinoma but that in the functioning, surrounding thyroid parenchyma, which fails to respond to T_3 suppression. Namely, the hot area on the scan represents a complex of the carcinoma and the surrounding parenchyma. The size of the complex is larger than that of the carcinoma. Thus, it is understandable that the size of the area of increase uptake on the scan is much larger than the 1.5 cm carcinoma.

Our patient was euthyroid as reflected by normal TSH concentration and normal TSH response to TRH. A T_3 suppression test, however, demonstrated that the thyroid had autonomous function. In this respect, we emphasize the necessity of a T_3 suppression test to evaluate thyroid function, especially in patients with euthyroidism.

The occurrence of Graves' ophthalmopathy without hyperthyroidism is designated as euthyroid Graves' disease. Upper lid retraction is an important clinical feature in differentiating Graves' ophthalmopathy from other causes of proptosis where the lid is usually pushed forward with the globe, and not retracted (*21*). In unilateral cases, orbital pseudotumor is the most frequent differential. Graves' ophthalmopathy generally has a gradual, painless onset. In contrast, orbital pseudotumor usually has an abrupt, painful onset. In ophthalmopathy, MRI demonstrates enlarged eye muscles, usually with their slender tendons. In contrast, orbital pseudotumor usually has involvement of a single eye muscle, with enlargement of both the muscle and its tendon. The data from this patient were believed to be sufficient to make the diagnosis of an autonomously functioning thyroid carcinoma associated

Most solitary autonomously functioning thyroid nodules (AFTN) are nontoxic. Nontoxic AFTN is usually left untreated for the following reasons (*22*): (a) progression from the nontoxic to the toxic stage occurs in only a small fraction of patients; (b) the pronounced tendency toward spontaneous degeneration reduces the likelihood of future toxicity; (c) the scintigraphic finding characterized by being "hot" is generally supposed to indicate the absence of malignancy since thyroid carcinoma presenting a hot nodule is extremely rare.

In conclusion, despite the great likelihood of a hot nodule being benign, the possibility of carcinoma should not be overlooked, and a cautious approach is recommended.

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