Papillary Thyroid Carcinoma without Metastases Manifesting as an Autonomously Functioning Thyroid Nodule

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Abstract. A 59-year-old woman with papillary thyroid carcinoma inside of an autonomously functioning thyroid nodule is described in this report. The patient was referred to our clinic because of rapid weight loss and swelling on the left side of the neck. Ultrasonography of the thyroid demonstrated a nonhomogeneous nodule in the lower part of an enlarged left lobe. Both $^{99m}$Tc and $^{123}$I thyroid scintigraphic imaging showed a hot area corresponding to the nodule with lower uptake in the remaining thyroid tissue. Histopathological examination of the nodule revealed papillary adenocarcinoma, and the immunohistochemistry proved weak but positive staining for triiodothyronine and thyroxine. Based on these findings, the nodule was diagnosed as a functioning papillary adenocarcinoma. Although thyroid carcinoma manifesting as a hot nodule on the radionuclide isotope scan is an extremely rare occurrence, the current case is clinically important because it suggests that the diagnosis of a hot nodule cannot always rule out thyroid carcinoma in the nodule, and that even a hot nodule requires careful management so that the malignancy is not overlooked.

Key words: Papillary thyroid carcinoma, Hyperfunctioning thyroid carcinoma, Hot nodule, Autonomously functioning thyroid nodule, Metastasis

(HYPERTHYROIDISM due to thyroid carcinoma is a rare but well-recognized clinical phenomenon [1, 2]. This situation has been generally described as the result of excessive production of thyroid hormone by extensive metastatic lesions [2–8]. On the other hand, a nonmetastatic hyperfunctioning thyroid carcinoma is extremely rare [1, 2, 9, 10]. Therefore, it is commonly believed that the diagnosis of a solitary autonomously functioning thyroid nodule (AFTN), a solitary “hot” nodule on radionuclide imaging, can almost always rule out malignancy in the nodule [1, 9, 10]. However, in a very few cases, solitary hot nodules do harbor malignancy [1, 2, 9, 10].

In this report, we present a rare case of papillary carcinoma without metastases manifesting as an AFTN.

Case Report

A 59-year-old Japanese woman was first referred to Otowa Clinic on 3 December 2002 because of rapid loss of weight and an enlarged painless mass on the left side of neck. She had noticed the enlarged neck mass five years earlier, and complained of compressive neck
symptoms, but no dysphagia, hoarseness, or shortness of breath. Despite a good appetite, she lost 7 kg of body weight (from 50 kg to 43 kg) over the past 3 months. Other signs or symptoms of hyperthyroidism were not present. She had neither a family history of thyroid diseases nor a past history of radiation to the head or neck.

On physical examination, her blood pressure and pulse were normal. An enlarged painless mass (approximately 9 cm) with an irregular surface was palpated on the anterior left side of her neck. A nontender and rather hard nodule (approximately 2 cm) was palpable within the lower part of the neck mass. No lymph nodes were palpable in the neck or supraclavicular region. Physical examination was otherwise unremarkable.

Ultrasonography of the thyroid revealed a diffuse enlargement of the left lobe with a mild hypoechoic pattern, and a poorly-demarcated nonhomogeneous nodule with cystic degeneration and calcification, measuring 1.5 cm at the lower end of the left lobe (Fig. 1 A, B). Neck CT scan showed some tracheal deviation to the right without narrowing the airway.

Routine laboratory data showed no abnormality. However, thyroid function tests showed elevated free triiodothyronine (T3) of 4.4 pg/ml (normal; 2.4–4.3 pg/ml) and free thyroxine (T4) of 2.7 ng/dl (normal; 0.8–2.1 ng/dl), and undetectable thyroid-stimulating hormone (TSH) of <0.01 µIU/ml (normal; 0.24–3.70 µIU/ml). Serum thyroglobulin was 520.0 ng/ml (normal; <45 ng/ml). Thyroid stimulating antibody (TSAb), anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) antibodies, and TSH receptor antibody (TRAb) were all negative.

A thyroid technetium-99m (99mTc) scintigram demonstrated a hot area, with no cold area inside, corresponding to the nodule in the left lower lobe (Fig. 2). Three-hour and 24-hour radioactive iodine thyroid uptakes were 5.00% (normal: 5–15%) and 13.54% (normal: 10–40%), respectively. A thyroid iodine-123 (123I) scintigram also showed a hot area corresponding to the thyroid nodule, with lower uptake in the remaining thyroid tissue (Fig. 3).

Fine needle aspiration biopsy (FNAB) of the nodule was performed. Atypical cells which had large nuclei with a pale ground-glass appearance were found in biopsy specimens from the nodule. The nodule was interpreted as a papillary adenocarcinoma. No malignancy was detected by FNAB of the enlarged left lobe.
except in the nodule. She received Lugol’s solution for 5 days immediately before the operation. A left thyroid lobectomy and isthmectomy were performed on 16th January 2003. At neck exploration, the enlarged left lobe was diffusely elastic and soft, and did not show either adhesion or invasion to the surrounding tissue. The left lobe, the isthmus and the paratracheal lymph nodes were removed, and the left recurrent laryngeal nerve was preserved.

Postoperative histological examination revealed a papillary adenocarcinoma situated within the nodule of the left lower lobe (Fig. 4A). Macroscopically, the nodule was whitish, measuring 1.5 cm in diameter (Fig. 5). It was relatively well circumscribed but not encapsulated, had a granular appearance, and bulged on the thyroid surface (Fig. 5). Microscopically, the

![Fig. 4. (A) Histologic appearance of the thyroid tumor demonstrating papillary structures with a follicular pattern (Hematoxylin-eosin stain; × 100). (B) The nuclei of the carcinoma cells showing characteristic nuclear features seen in papillary adenocarcinoma, specifically, ground-glass nuclei, grooves, and pseudoinclusions (Hematoxylin-eosin stain; × 400).](image)

![Fig. 5. Cross-section through the left thyroid lobe.](image)

![Fig. 6. Immune staining for T3 (A) and T4 (B) showing that the immunohistochemical examination of the neoplastic tissue was weakly but still rather convincingly positive for T3 and T4 (× 200).](image)
nodule contained mainly carcinoma cells but there were also islands of scattered, normal small follicles, interstitial fibrosis, and hyalinization. Malignant growth of carcinoma cells (approximately 1.0 cm) with other multiple small foci of carcinoma cells within the nodule did not infiltrate the tissue outside the nodule, and showed a papillary structure suggestive of papillary carcinoma. The nuclei of the carcinomatous cells had the characteristic nuclear features seen in papillary carcinoma: ground-glass nuclei, grooves, and pseudo-inclusions (Fig. 4B). The surrounding thyroid tissue showed a macrofollicular architecture with no evidence of lymphocytic infiltration identified. No histologic evidence of Graves’ disease, or Hashimoto’s disease, or malignancy was found. The result of immuno-histochemical examination of the carcinomatous cells in the nodule was weakly but still definitely positive for T3 and T4 (Fig. 6 A, B). No metastatic foci were recognized in the four resected lymph nodes.

Postoperatively she had mild and transient hypocalcemia which normalized without medication in 1 week. Her TSH has been kept around 0.5 μU/ml with 25 μg of levothyroxine daily. Three months postoperatively, her weight came back to 48 kg. No other complications have occurred in the patient’s postoperative course so far.

Discussion

Our patient presented with a palpable thyroid nodule in an enlarged left thyroid lobe and hyperthyroidism with the absence of TSAb, TRAb, TgAb, and TPOAb. Despite undetectable TSH levels, both 99mTc and 123I thyroid scintigraphic imaging showed a hot nodule corresponding to the nodule, with lower uptake in the remaining thyroid tissue. The nodule was considered to be AFTN, which is a rare condition representing a low percentage of all solitary thyroid nodules (varying from 6% to 20%) [11, 12]. FNAB and postoperative histopathological examination showed the nodule to be a papillary adenocarcinoma, whereas the extranodal tissue of the left thyroid lobe showed a macrofollicular architecture with no evidence of lymphocytic infiltration or malignancy, and was considered a simple goiter, which is defined as noninflammatory, nonneoplastic, diffuse or nodular enlargement of the thyroid gland without causing hyperthyroidism [13, 14].

The major determinant for thyroid growth has long been considered to be the TSH level [13]. However, this is inconsistent with the observation that the serum TSH concentration is normal in most patients with nontoxic goiter [13, 15]. In our case, regression of the goiter was not found regardless of suppressed TSH. Therefore, higher TSH levels as the sole factor responsible for goiter appears to be an oversimplification [13]. Goiter should be regarded as a complex trait in which genetic susceptibility [13, 16], environmental factors [13], TSH, growth factors [13, 17, 18], and angiogenic substances [13, 19, 20] either play a distinct and separate role or act synergistically through complex interaction mechanisms [13]. However, the relative contributions of these factors to the goitrogenic process have yet to be clarified [13].

It should be noted in our case that the papillary thyroid carcinoma found was as an AFTN. The incidence of thyroid carcinoma in a hot nodule is reported to be low by most authors [1, 2, 9, 10, 21, 24, 25, 27, 28], but is somewhat higher in other retrospective studies (Table 1) [22, 23, 26, 27, 30]. Actually, thyroid carcinoma in a hot nodule has been described in numerous case reports [3–8, 11, 12, 31–46], as well as in ours. However, unlike our case, most of these cases show a cold area within a hot nodule as Tsuboi et al. [42] mention in their report, indicating that the thyroid carcinoma itself did not produce thyroid hormone. Hyperfunctioning thyroid carcinoma is thus considered even more infrequent. In addition, hyperfunctioning thyroid carcinoma has been described generally due to extremely extensive functioning metastases [2–8], most

<table>
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<th>Author and year</th>
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<th>Hot nodule</th>
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<tr>
<td></td>
<td>the number</td>
<td>the incidence</td>
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<td>Ito and Mimura</td>
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<tr>
<td>Croom et al.</td>
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<tr>
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<td>Ahiuya et al.</td>
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<td>Mizukami et al.</td>
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<td>(9)</td>
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<td>Gabriele et al.</td>
<td>2003</td>
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Parentheses means inclusion of thyroid carcinoma nearby (outside) the hot nodule.
of which have almost always been follicular carcinoma [2, 8]. No less than 50 such cases have been described in the literature, and are well summarized by Paul and Sisson [2]. In their review of 48 cases, distant metastases were present in 83.3% of the patients, with follicular carcinoma in 89.6% of them.

On the other hand, the carcinoma presenting as AFTN in this case was a nonmetastatic hyperfunctioning papillary thyroid carcinoma. Some authors maintain that, in the reported cases of carcinoma presenting as an AFTN, the carcinoma is only incidentally located in a hot nodule [1, 23]. However, in our case, the immunohistochemical study of the carcinoma cells was positive for both hormones T3 and T4. Scintigraphically our case did not have a cold area within the hot nodule, although we cannot rule out the possibility that the carcinoma in our case might have been too small or too localized to exhibit cold lesion. These findings suggest that our case is not a coincidental association of hyperthyroidism and carcinoma but a rare hyperfunctioning papillary thyroid carcinoma.

Rosa et al. [12] reviewed 17 cases such as ours in 1990. To our knowledge, there are now 25 cases of nonmetastatic thyroid carcinoma mimicking an AFTN described in the literature (Table 2) [11, 12, 31–46]. Women were far more often affected than men (ratio female/male = 22/3), but there was no significant peak period with regard to age. Interestingly, the histological finding of these tumors was principally papillary carcinoma [12, 31–38, 42, 43, 45, 46], as opposed to that of metastatic functioning carcinomas predominantly being follicular type [2]. This is in agreement with our case.

The reason why these carcinomas were able to produce excessive hormone without extensive metastases may be due to the gene mutations reported to occur in AFTN, including mutations of G protein α chain (Gsα) gene and TSH receptor gene with associated elevated intracellular cAMP [47]. Russo et al. [48] reported the first case of an activating mutation of the TSH receptor gene in an autonomously hyperfunctioning thyroid carcinoma. By contrast, Bourasseau et al. [49] denied TSH receptor and Gsα/g9/g32 gene mutation in hyperfunctioning thyroid carcinoma. Further studies are thus needed to clarify these issues.

Clinically, it is important to predict the incidence of

<table>
<thead>
<tr>
<th>Case No.</th>
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<th>Clinical state</th>
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<td>9</td>
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malignancy in hot thyroid nodules. The classical benign AFTN often occurs in the 30s or 40s, has a history of long-standing and slowly expanding mass in the neck, and usually presents as a smooth, well-defined, round or ovoid mass that is firm and moves freely [9, 50]. In our case, AFTN occurred at a somewhat older age compared with the classical benign AFTN, but otherwise there were no significant differences. Among patients with classical AFTN, about 20 percent have thyrotoxicosis; these are mostly patients 40 years of age or older with a nodule 2.5 cm or more in diameter [9, 50]. However, in our case, the nodule was smaller in diameter, and the patient was 59 years old. In addition the hyperthyroidism of classical AFTN is generally milder than that of Graves’ disease and, as in our case, is notable for the absence of infiltrative orbitopathy and myopathy [50]. Reports in the literature [9] indicate significant difficulty in determining the risk that AFTN will undergo malignant degeneration. However, some clinical findings are reported as the risk factors for malignancy: Age <20 or >60 years, male sex, a family history of medullary or papillary thyroid cancer or of familial adenomatous polyposis (Gardner’s syndrome), a past history of head or neck radiation, rapid tumor growth, irregular outline, fixation to adjacent structures, symptoms of tumor invasion, and metastases such as enlarged regional lymph nodes [2, 9, 12, 45]. On the other hand, young women, an excessive production of T3, and conflicting results between 99mTc and 123I scintigram have been reported as unique risk factors of malignancy in a hot nodule [12, 51].

In actual practice, however, few patients have these symptoms, and most nodules are nearly asymptomatic, as in our case [9, 12]. In the case of metastatic thyroid carcinoma, hot nodules outside the thyroid can be helpful in diagnosis of malignancy. But, especially in the case of nonmetastatic hyperfunctioning thyroid carcinoma, it is somewhat difficult at present to predict the existence of malignancy in the hot nodule. Therefore, FNAB, which is safe, inexpensive, and particularly useful for the diagnosis [9, 12, 28, 37], should be performed in a hot as well as cold thyroid nodule [12, 28, 37].

The clinical course of a non-metastatic hyperfunctioning thyroid carcinoma seems to depend on its histologic features, patient’s age, and tumor stage at the time of diagnosis [52], but there is still little information available in the literature [12]. It seems that prognosis of metastatic follicular thyroid carcinoma is not different with or without hyperthyroidism [2, 53]. However, the prognosis of non-metastatic hyperfunctioning papillary thyroid carcinoma was not fully described in the literature. Recently, Als et al. [54] reported the survival analysis of 19 patients with hyperfunctioning thyroid carcinoma. They showed that five-year survival rates for hyperfunctioning thyroid carcinoma (n = 19, 56%) and differentiated thyroid carcinoma (n = 545, 94.5%) differed significantly (hazard ratio 4.8, p = 0.001), although the difference was attenuated by matching for age, sex, and histopathologic type. But in their study, metastatic carcinoma and nonmetastatic carcinoma were dealt with at the same time, because hyperfunctioning thyroid carcinoma was diagnosed when scintigraphic hot thyroid areas were attributable to the thyroid carcinoma and/or total thyroidectomy failed to induce hypothyroidism. Hence, their report does not present enough information about the prognosis of nonmetastatic hyperfunctioning thyroid carcinoma, which we have discussed in this paper.

In conclusion, our case is pathophysiologically interesting when we consider that a papillary thyroid carcinoma could produce hyperthyroidism without metastases, and clinically it is important in suggesting that malignancy cannot always be excluded even in a hot thyroid nodule, and that all thyroid nodules, whether cold or hot, require careful management so that malignancy is not overlooked.

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