Papillary Thyroid Carcinoma Manifesting as an Autonomously Functioning Thyroid Nodule

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Hyperfunctioning thyroid carcinoma is very rare. Hence, radionuclide imaging of thyroid hot nodules usually suggests a benign tumor, and less than 4% of cases have been reported as malignant. We would like to present a case of a hyperfunctioning papillary thyroid carcinoma that was initially treated with radioactive iodine. A 58-year-old woman was referred to our hospital for palpable thyroid nodule and a 5-kg weight loss within 6 months. Thyroid function test revealed thyrotoxicosis, and thyroid autoantibodies were absent. 99mTc thyroid scintigraphy showed a 2 x 2 cm-sized hyperactive hot nodule at the left lobe. Despite radioactive iodine treatment with a dose of 10 mCi 131I, thyroid function did not improve. Fine needle aspiration revealed papillary thyroid cancer. The patient underwent total thyroidectomy. Although clinical features and thyroid scans suggest a benign nodule, the possibility of malignancy should not be ruled out. Malignant thyroid hot nodules are rare; however, its possibility should be taken into account. Therefore, we suggest that ruling out malignancy by existing diagnostic guidelines can misdiagnose even a typical case with benign features. As thyroid nodule detection is getting sensitive and accurate, we present this case to discuss whether additional diagnostic approaches would be necessary for thyroid nodules. (Endocrinol Metab 27:59-62, 2012)

Key Words: Thyroid nodule, Papillary thyroid cancer

INTRODUCTION

Thyroid nodule is common disorder which occurs in about 3-7% of adults by physical examination, and 6-20% of nodules present autonomously functioning thyroid nodule [1]. When thyroid scintigraphic imaging reveals hot uptake, it is generally accepted as benign feature because malignancy is very rare in hot nodule [2,3]. From the existing guideline, fine needle aspiration biopsy is not recommended for hot nodule, and treatment should be started with iodine ablation. In this report, we present a rare case of malignant thyroid hot nodule which had been treated with radioactive iodine without success.

CASE REPORT

A 58-year-old female patient visited to Soonchunhyang University Hospital because of 5 kg of weight loss during last 6 months. Her weight was 50.1 kg, height 157.5 cm and body mass index 20.2. She didn’t have any family history of thyroid cancer and radiation exposure, and she didn’t complain any typical symptoms as palpitation, sweating or general weakness. On physical examination, a palpable 2 x 2 cm sized mass was found on left lobe of the thyroid, and the laboratory investigation showed: T3 2.77 ng/mL (0.8-2), free T4 2.91 ng/dL (0.93-1.7), thyroid stimulating hormone (TSH) 0.006 μIU/mL (0.27-4.2), anti-thyroglobulin antibody 10.11 IU/mL (0-115), anti-thyroperoxidase antibody 15.86 IU/mL (0-34). The same day, 99mTc thyroid scintigraphy was performed, and the hyperactive hot nodule was found in the left lobe (Fig. 1). We considered that functioning hot nodule was the cause of thyrotoxicosis, so the patient underwent the radioiodine treatment with dose of 10 mCi 131I. After the treatment we follow-up the thyroid hormone every 2 months, after 6 months thyroid function test showed: T3 1.93 ng/mL, free T4 2.91 ng/dL (0.93-1.7), thyroid stimulating hormone (TSH) 0.006 μIU/mL (0.27-4.2), anti-thyroglobulin antibody 10.11 IU/mL (0-115), anti-thyroperoxidase antibody 15.86 IU/mL (0-34).
3.2 ng/dL, TSH 0.006 μIU/mL. Then we decided to add methimazole 10 mg and thyroid ultrasonography was performed. It showed ill defined hypoechoic nodule in the left lobe, 1.7 × 1.8 cm in size, with normal echogenicity in the remaining thyroid gland (Fig. 2). After that she transferred to local hospital for personal reason, and fine needle aspiration was performed. The result revealed papillary thyroid carcinoma, so she referred to our hospital again, and total thyroidectomy was performed.

Postoperative histological examination revealed papillary carcinoma in the left lobe. Macroscopically, the nodule was 2 × 1.5 sized, and surface was smooth and ill defined, gray-white solid mass. Microscopically, the nodule showed papillary thyroid carcinoma and surrounding thyroid tissue was normal architecture without any histological evidence of Graves’ disease (Fig. 3). Surgical margin was clear and twenty-six resected lymph nodes showed no evidence of metastasis. After the operation the patient showed no complications except mild transient hypocalcemia. The patient took a 150 μg of levothyroxine for 4 months, and the thyroid function changed as follows, T3 1.2 ng/mL, free T, 2.35 ng/dL, TSH 0.034 μIU/mL, anti-thyroglobulin antibody 13.37 IU/mL (0-115), and thyroglobulin was 0.1 ng/mL (5-25).

We did mutation analysis with thyroid tissue sample using real time polymerase chain reaction. We used PNAClamp B-raf Mutation Detection Kit and PNAClamp K-ras Mutation Detection Kit (Panagen Inc., Daejeon, Korea) which are using peptide nucleic acid for amplification. And the result showed BRAF mutation, while RAS mutation was absent (Fig. 4).

**Fig. 1.** Thyroid 99mTc scintigraphy shows a hot nodule in the left lobe while remaining areas shows minimal activity.

**Fig. 2.** Thyroid ultrasonography reveals a 1.8 × 1.2 × 1.7 cm sized ill-defined hypo echoic nodule in left thyroid lobe.

**Fig. 3.** Histology of the resected thyroid nodule. A. Histology demonstrates the papillary structure with ill defined margin (H&E stain, × 40, thyroid). B. The large hyperchromic nuclei with central core and groove are compatible with papillary thyroid carcinoma (H&E stain, × 400, thyroid).
Autonomously Functional Papillary Thyroid Carcinoma

DISCUSSION

Thyroid nodule is a common disorder which occurs in about 3-7% of adults by physical examination, and 6-20% of nodules present autonomously functioning thyroid nodule [1]. When thyroid scintigraphic imaging reveals hot uptake, it is generally accepted as benign feature because malignancy is very rare in hot nodule [2,3]. From the existing guideline, fine needle aspiration biopsy is not recommended for hot nodule, and treatment should be based on thyroid functional status.

However, recent studies have been reporting the several cases of hyperfunctioning nodule which revealed as malignancy [3,4]. The incidence of thyroid carcinoma in a hot nodules is reported to be low in most literatures [2-5]. Mizukami et al. [5] presented that the incidence of hyperfunctioning thyroid cancer was variable from 0.4% to 11.8%, these data were based on ten reports which published from 1983 to 2003.

The mechanism of producing excessive hormone from thyroid cancer has not been established, but it is assumed that G protein α chain (Gsα) and TSH receptor gene mutation may contribute to the abnormal hormone production [4,6]. The pathogenesis of hyperfunctioning thyroid nodule has been revealed that mutated TSH receptor increases the intracellular c-AMP which stimulates the cell growth with excessive hormone production.

BRAF, RAS, and RET mutations are well known oncogenes of papillary thyroid carcinoma, that activate the signaling pathway in thyroid follicular cells and stimulate the tumor progression [6]. Many hormones, cytokines and growth factors control thyroid follicular cell growth through the intracellular signaling system. As RET-RAS-BRAF system is one of main pathway controlling cell cycle, it can stimulate abnormal activation of cell cycle followed by thyroid carcinoma. And most papillary thyroid cancer has at least one of the RET-RAS-BRAF mutation [7].

Therefore, it can be hypothesized that autonomously hyperfunctioning thyroid nodule found to be papillary thyroid carcinoma may contain several combined gene mutations described above. And also several factors including genetic susceptibility, environmental factors, TSH, growth factors, and angiogenic substances either play a distinct and separate role or act synergistically through complex interaction mechanism.

In this case, gene analysis showed BRAF mutation, while RAS mutation was absent (Fig. 4).

The exact mechanisms of hyperfunction of thyroid carcinoma are still unclear. But it is obvious that TSH receptor gene and other oncogenes may be involved. So we need further studies to explore any relationship between oncogenes (RET-RAS-BRAF) leading to thyroid malignancy and other gene mutations (Gsα and TSH receptor gene) causing abnormal hormone production.

The limitation of the presenting case was failure to get TSH receptor and Gsα gene analysis. We just assume that BRAF mutation was the oncogene for papillary thyroid carcinoma in this patient.

Granter et al. [8] reported nuclear changes suggestive of papillary thyroid carcinoma in thyroid nodule after 131I treatment. And thyroid carcinomas appeared after radioactive iodine treatment for hyperthyroidism have been reported [8]. However in other studies no malignant change was observed, either clinically or cytologically after radioactive iodine treatment. The oncogenic effect of radioactive iodine treatment has yet to be proven. In our case, since only several months had passed after the 131I treatment, we assume that the autonomous nodule was already malignant at presentation. The latent period of the carcinoma cases after radioactive iodine treatment was generally longer than 3 years with mean of 11.4 years [9].

Hyperfunctioning thyroid carcinoma is extremely rare. So it is generally believed that the diagnosis of hot nodule on radionuclide imaging can almost always rule out malignancy in thyroid nodule. However when nodule shows suspicious malignant features, it is important not to exclude the possibility of malignancy, so we rec-
ommend to check thyroid ultrasonography and fine needle aspiration biopsy when needed [3]. As the number of malignant hot nodules is getting increased we should consider setting up the appropriate diagnostic tool for it. And, of course, whether the nodule is cold or hot, we need to approach carefully and start the proper management not to overlook the possibility of the malignancy.

요 약

자율 기능성 감상선암은 매우 드문 것으로 알려져 있다. 감상선 결 점이 발견되었을 때 감상선 스캔상에서 기능성 결절의 양 상을 나타내는 경우 대개 양성 종양을 시사하며 4% 미만에서 악성 종양으로 보고된 바 있다. 이는 뿐만 아니라 방사선 요소 치료를 받은 기능 성 감상선 결절 환자에서 유두 감상선암이 진단되어 이를 보고하려 한다. 58세 여자 환자가 6개월간의 5 kg의 체중 감량으로 인한 병원 을 찾아다가 감상선 결절이 진단되어 본원으로 전원 되었다. 내원시 감상선호르몬은 T3 1.93 ng/mL, free T4 3.2 ng/dL, TSH 0.006 μIU/mL로 확인되었고 감상선 자가항체 검사는 모두 정상 범위 내로 확인되었다. ¹³¹I 감상선 스캔을 시행한 결과 2 × 2 cm 크기의 열결절이 원암에서 발견되었다. 환자는 기능성 감상선 결절로 진단 하에 10 mCi ¹³¹I로 방사선 요소 치료를 시작하였으나 6개월 후에도 감 상선 기능은 호전을 보이지 않았고 추가적으로 시행한 세침흡인검 사에서 유두 감상선암으로 진단되어 감상선 전절제술을 시행 받은 사례이다. 이는 뿐만 아니라 방사선 요소 치료를 받은 환자에서 양성 결절로 의심된 경우가 많으므로 악성 결절의 가능성을 완전히 배제할 수 없으며, 감상선 결절의 평가에 있어 기존의 진단 가이드라인반 전적으로 의존하여 평가할 시 잘못된 진단을 할 수 있음을 보여준다. 감상선암의 발병 증가에 따라 감상선 결절에 대한 관심 및 검사 가 점점 증가하는 추세이다. 따라서 감상선 결절의 정확한 평가를 위한 진단 가이드라인의 재정립이 필요하다.

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