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CASE REPORT

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. ^{99m}Tc thyroid scintigraphy showed a 2 × 2 cm-sized hyperactive hot nodule at the left lobe. Despite radioactive iodine treatment with a dose of 10 mCi ^{131}I, 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 × 2 cm sized mass was found on left lobe of the thyroid, and the laboratory investigation showed: T_3 2.77 ng/mL (0.8-2), free T_4 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, ^{99m}Tc 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 ^{131}I. After the treatment we follow-up the thyroid hormone every 2 months, after 6 months thyroid function test showed: T_3 1.93 ng/mL, free T_4

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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 echogenecity 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, T_3 1.2 ng/mL, free T_4 2.35 ng/dL, TSH 0.034 μIU/mL, antithyroglobulin 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 (Panagene Inc., Daejeon, Korea) which are using peptide nucleic acid for amplification. And the result showed BRAF mutation, while RAS mutation was absent (Fig. 4).

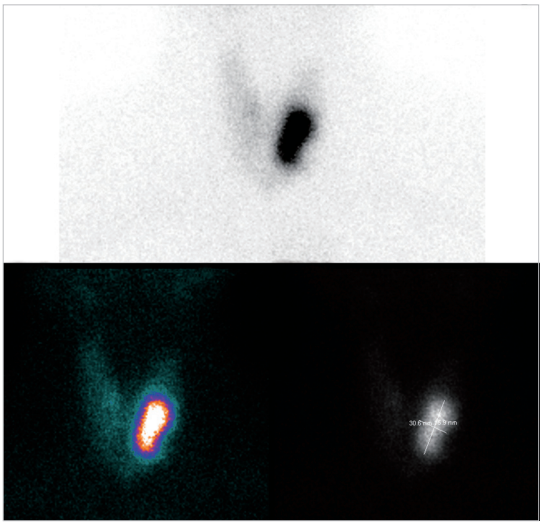

Fig. 1. Thyroid ^{99m}Tc scintigraphy shows a hot nodule in the left lobe while remaining areas shows minimal activity.

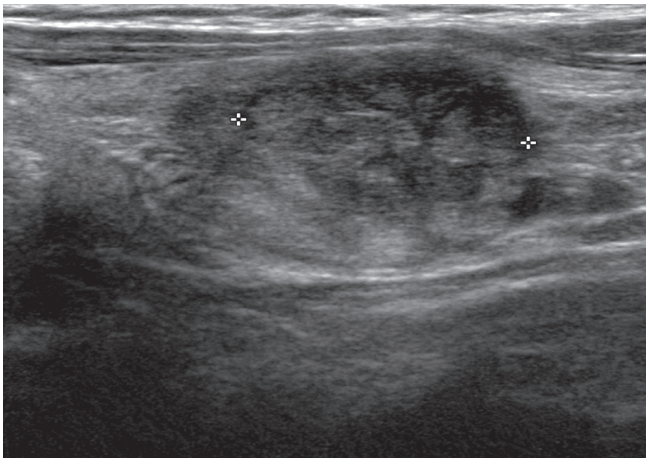

Fig. 2. Thyroid ultrasonography reveals a 1.8 × 1.2 × 1.7 cm sized ill-defined hypo echoic nodule in left thyroid lobe.

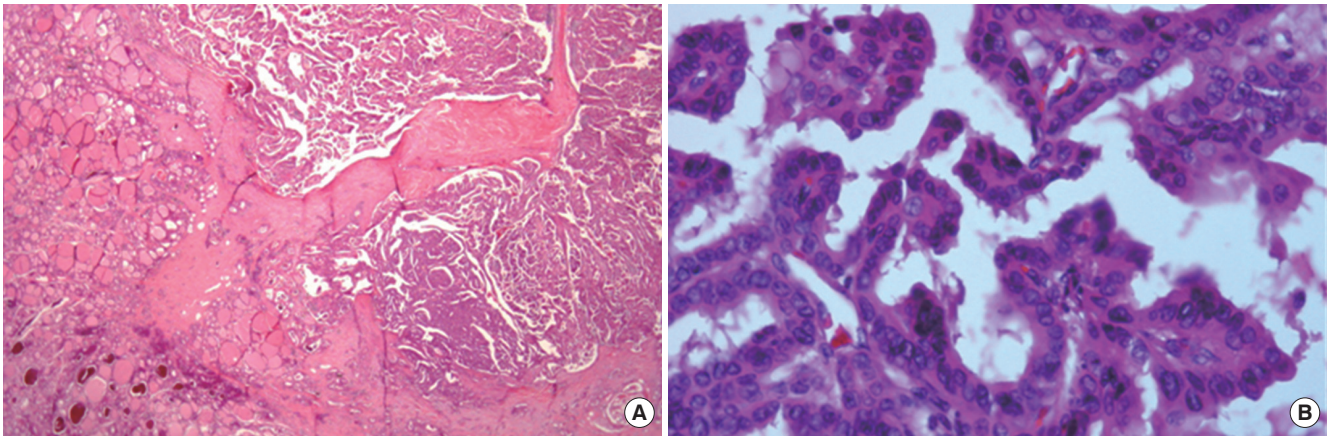

Fig. 3. Histology of the resected thyroid nodule. A. Histology demonstrates the papillary structure with ill defined margin (H&E stain, × 40, thyroid). B. The large hyperchromic nuclei with central core and groove are compatible with papillary thyroid carcinoma (H&E stain, × 400, thyroid).

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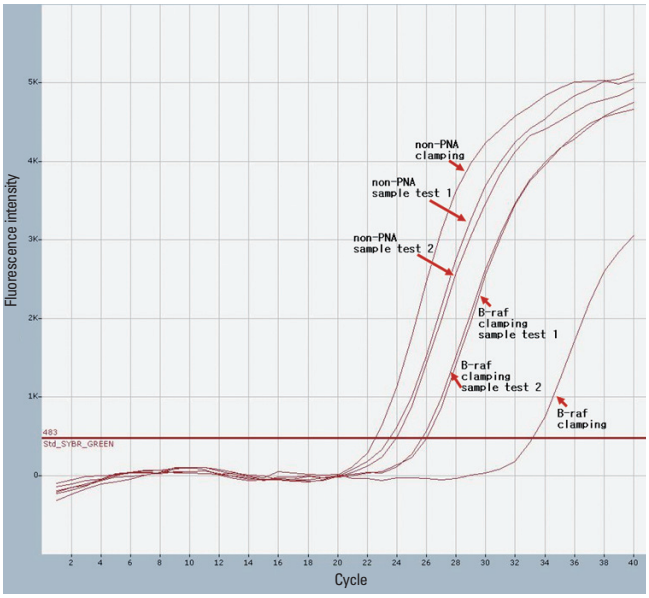

Fig. 4. Gene analysis using real time polymerase chain reaction (PNAClamp B-raf Mutation Detection Kit) presents amplified B-raf mutation like other sample studies. PNA, peptide nucleic acid.

DISCUSSION

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 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 ^{131}I 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 ^{131}I 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 nodule 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 갑상선암은 매우 드문 것으로 알려져 있다. 갑상선 결절이 발견되었을 때 갑상선 스캔상에서 기능성 결절인 열결절의 양상을 나타내는 경우 대개 양성 종양을 시사하며 4% 미만에서 악성 종양으로 보고된 바 있다. 이번 증례는 방사성 옥소 치료를 받은 기능성 갑상선 결절 환자에서 유두 갑상선암이 진단되어 이를 보고하려 한다. 58세 여자 환자가 6개월간의 5 kg의 체중 감량으로 인근 병원을 찾았다가 갑상선 결절이 촉진되어 본원으로 전원 되었다. 내원시 갑상선호르몬은 T_3 1.93 ng/mL, free T_4 3.2 ng/dL, TSH 0.006 μIU/mL로 확인되었고 갑상선 자가항체 검사는 모두 정상 범위 내로 확인되었다. ^{99m}Tc 갑상선 스캔을 시행한 결과 2 × 2 cm 크기의 열결절이 왼엽에서 발견되었다. 환자는 기능성 갑상선 결절로 진단 하에 10 mCi ^{131}I으로 방사선 옥소 치료를 시작하였으나 6개월 후에도 갑상선 기능은 호전을 보이지 않았고 추가적으로 시행한 세침흡인검사에서 유두 갑상선암으로 진단되어 갑상선 전절제술을 시행 받은 사례이다. 이번 증례를 통해서 임상 양상과 갑상선 스캔상에서 양성 결절로 의심이 된다 하더라고 악성 결절의 가능성을 완전히 배재할 수 없으며, 갑상선 결절의 평가에 있어 기존의 진단 가이드라인에만 전적으로 의존하여 평가할 시 잘못된 진단을 할 수 있음을 보여준다. 갑상선암의 발병 증가에 따라 갑상선 결절에 대한 관심 및 검사가 점점 증가하는 추세이다. 따라서 갑상선 결절의 정확한 평가를 위한 진단 가이드라인의 재정립이 필요하다.

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