Metastatic Papillary Thyroid Carcinoma in an Autonomous Hyperfunctioning Thyroid Nodule in an Adolescent: Case Report and Literature Review

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Rec date: Feb 26, 2014, Acc date: Apr 28, 2014, Pub date: May 01, 2014

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Abstract

**Background:** Although thyroid nodules are less common in children and adolescents, the malignancy rate for nodules is higher among children and adolescents than adults. A nodule that is discovered in a patient presenting with hyperthyroidism is usually a benign nodule or benign toxic adenoma and, thus, nodules are biopsied only infrequently.

**Objective:** To report a case of papillary thyroid carcinoma presenting with a hyperfunctioning (hot) thyroid nodule.

**Case report:** A 14-year-old female presented with symptoms of thyrotoxicosis and multi-nodular goitre. Laboratory findings were consistent with the diagnosis of thyrotoxicosis. Thyroid ultrasonography showed an enlarged thyroid gland with cystic and solitary nodules, diffuse heterogeneous echo, and microcalcifications. Doppler scans revealed increased vascularity within the left thyroid lobe and a solitary nodule. Thyroid scintigraphy revealed an autonomous nodule. Cytological examination of fine-needle aspirations from the solid nodule and left thyroid lobe revealed papillary thyroid carcinoma. The patient underwent total thyroidectomy. Histopathology of the thyroid gland and lymph nodes were also consistent with papillary thyroid carcinoma with nodal metastases.

**Conclusion:** Contrary to the guidelines published by major endocrine societies, the detection of an autonomously functioning thyroid nodule in children and adolescents does not exclude the possibility of thyroid carcinoma. Suspicious hot nodules should be evaluated cytologically.

**Keywords:** Autonomously hyperfunctioning thyroid nodule (AHTN); Thyrotoxicosis; Papillary thyroid carcinoma; Thyroid ultrasonography; Children; Adolescent

Introduction

Although thyroid nodules occur less frequently in children and adolescents than adults, they are more often malignant compared with those observed in older patients [1-4]. Therefore, a major goal of the diagnostic evaluation of thyroid nodules is to differentiate thyroid cancers from benign adenomas. A number of features raise suspicion of malignancy. According to the algorithms reported by the major endocrine societies, a fine needle aspiration biopsy (FNA) is not necessary for the management of thyroid nodules in children in the presence of suppressed thyroid-stimulating hormone (TSH) levels and a hot nodule [1-4]. However, with the advent of high-resolution ultrasonography, 77 cases of biochemically-hyperthyroid patients with autonomous functioning thyroid nodules (AHTN) were discovered to harbor differentiated thyroid carcinoma [5]. Only 11 of these patients were children or adolescents, and there was a higher prevalence of papillary type of cancer and female gender [5,6]. Here, we present an additional case of papillary thyroid carcinoma presenting with thyrotoxicosis in a 14-year-old female.

Case Report

A 14-year-old female presented to the local state hospital with heat intolerance, weight loss, palpitations, and insomnia for six months. Physical examination revealed an enlarged thyroid gland with a palpable nodule. She was referred to the Pediatric Endocrinology Division at the University Hospital of Eskisehir Osmangazi University because of thyrotoxicosis and nodular goiter symptoms. A detailed medical history revealed that she complained of weight loss (not quantified), nervousness, insomnia, fatigue, tremor, sweaty palms, heat intolerance, palpitations, and hair loss. Her past-medical history included a normal birth, several cases of enteritis, recurrent urinary tract and upper respiratory tract infections, a tonsillectomy at 5 years of age, and no history of previous radiation on her cervical region. Her family history revealed non-neoplastic thyroid disease.
On physical examination, she weighed 46 kg (10th percentile), her height was 155 cm (25th percentile), her body mass index was 19.1 kg/m², her blood pressure was 115/75 mmHg, and her heart rate was 115 beats per minute. Her skin was warm and moist. Her thyroid gland was enlarged, and there was a palpable non-tender 9×8×8 mm nodule in the lower right lobe and a non-tender 9×7×6 mm nodule in the left lobe. There was no evidence of cervical lymphadenopathy or thyroid bruit. She also had no exophthalmoses or lid lag. She had fine tremor of hands with normal bicep deep tendon reflexes bilaterally, and Tanner stage V breast development.

Thyroid function tests revealed that TSH level was undetectable (<0.001 mIU/mL, reference range, 0.4-4.5 mIU/mL), free triiodothyronine was 12.2 pg/mL (International System of Units [SI], 18.6 pmol/L; reference range, 2.3-4.4 pg/mL), and free thyroxin was 6.9 ng/dL (SI, 89 pmol/L; reference range, 0.7–1.8 ng/dL). Thyroid peroxidase antibody testing was negative (8.4 IU/mL, normal <10 IU/mL), as were thyroglobulin antibody (11 mIU/mL, normal <20 mIU/mL), and thyroid-stimulating hormone receptor antibody (<0.1 U/L, normal <1.0 U/L) tests. The thyroglobulin concentration was 112 μg/L (reference range, 2-35 μg/L). The thyroid ultrasonography (US) showed markedly enlarged right and left lobes, measuring 15×18×41 mm and 19×22×48 mm, respectively. There was a 9×8×8 mm nodule that included solid and cystic components in the right lower lobe with a homogenous parenchyma (Figure 1A), and a 9×8×7 mm solid nodule, multiple punctuate non-shadowing echogenic foci (Figure 1B, arrowheads) compatible with microcalcifications or psammoma bodies, and increased vascularity within the solitary nodule and left thyroid lobe (Figure 1C). 99mTc thyroid scintigraphy revealed a hyperactive nodule at the medial-lower segment of the left lobe accompanied by reduced activity in the remaining thyroid gland (Figure 1D). 131I scintigraphy confirmed the hyperactivity of the nodule, and the uptake of 131I at 24 h was 45% (normal reference, 15-35%).

Based on her clinical features, biochemical thyroid hormone levels, and imaging results, a diagnosis of autonomous hyperfunctioning thyroid nodule (AHTN) was made. Treatment with methimazole 0.2 mg/kg/24 h PO q8h and propranolol 2 mg/kg/24 hr PO q8h were started. She was euthyroid two months after starting the medical treatment. Because of the ultrasonographic signs on the left thyroid lobe, she was referred to the interventional radiology department for US-guided fine needle aspiration (FNA). The cytological investigation was positive for papillary thyroid carcinoma (PTC). After discussions with the parents and the patient, she underwent total thyroidectomy and excised cervical lymph node dissections. Histopathology of the thyroid gland and excised cervical lymph nodes confirmed the diagnosis of PTC and revealed lymph node metastases. The tumor cells showed characteristic nuclear features of PTC, including crowding or overlapping, occasional nuclear grooves, large and pale nuclei, and psammoma bodies (Figure 2A-D). Upon diagnosis of PTC, additional evaluation was performed. Chest X-ray and abdominal US showed no evidence of metastatic disease.

Six weeks after surgery, she was in frank hypothyroidism and underwent 131I radioactive ablation. A 125-mCi131I dose was administered; an 131I whole-body scan showed some uptake into the cervical area, and there was no evidence of metastatic disease.
Discussion

Although thyroid nodules generally occur less frequently in children and adolescents than in adults, the risk of malignancy is higher in the pediatric age group compared with adults [7,8]. Therefore, thyroid malignancy should be suspected when a thyroid nodule is found in children and adolescents because it has been reported that up to 20-25% of nodules in pediatric patients are malignant, compared with 5% in adults [1-4]. An increasing number of thyroid nodules in children have been discovered incidentally because of the widespread use of neck US. In addition, the vast majority of thyroid nodules occur in euthyroid conditions. The main objective of the diagnostic approach to thyroid nodules is to make a differential diagnosis as to whether a thyroid nodule is benign or malignant. This decision is made based on the patient’s past-medical history, family history, clinical presentation, and thyroid US characteristics. Clinical and ultrasonographic features of thyroid nodules that require FNA are summarized in (Table 1) [4,10-12].

| Nodule sonographic or clinical features | Recommended nodule threshold size for FNA |
|----------------------------------------|----------------------------------------|
| **High-risk history**                  |                                        |
| Nodule WITH suspicious sonographic features | >5 mm                                  |
| Nodule WITHOUT suspicious sonographic features | >5 mm                                  |
| Abnormal cervical lymph nodes           | Allc                                   |
| Microcalcifications present in nodule   | ≥1 cm                                  |
| Solid nodule                            |                                        |
| AND hypoechoic                          | >1 cm                                  |
| AND iso- or hyperechoic                 | ≥1–1.5 cm                              |
| Mixed cystic–solid nodule              |                                        |
| WITH any suspicious ultrasound features | ≥1.5–2.0 cm                            |
| WITHOUT suspicious ultrasound features  | ≥2.0 cm                                |
| Spongiform nodule                      | ≥2.0 cm                                |
| Purely cystic nodule                   | FNA not indicated                      |

Table 1: Sonographic and clinical features of thyroid nodules and recommendations for fine-needle aspiration (FNAs) (Adapted from the reference [4]). A) High-risk history; History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, 18FDG avidity on PET scanning; MEN2/FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL. MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid cancer. B) Suspicious features; microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view. C) FNA cytology may be obtained from the abnormal lymph node. D) Sonographic monitoring without biopsy may be an acceptable alternative.

Thyrotoxicosis is uncommon in children; the most common etiology is Graves’ disease which presents with diffuse goiter [13]. AHTN is an extremely rare etiology of thyrotoxicosis in children that is always diagnosed as a toxic adenoma. The guidelines and recommendations published by major endocrine societies recommend that malignant thyroid nodules typically do not take up radionuclides and appear cold, and that hyperfunctioning nodules on scintigraphy are almost always benign adenoma [1-4]. The American Thyroid Association (ATA) guidelines for patients with thyroid nodules recommend that no cytological evaluation is necessary for hyperfunctioning thyroid nodules [4]. Therefore, in hot nodules, thyroid US and cytological evaluation are not recommended routinely. Differentiated thyroid carcinoma may be a co-incidental finding in a case of thyrotoxicosis presenting with thyroid nodule [14]. However, papillary thyroid carcinoma was not a coincidental finding in our patient. The AHTN in the left thyroid lobe was confirmed using both biochemical parameters of thyrotoxicosis, and scintigraphic evidence of increased uptake of 131I and 99Tc. Thyroid US, particularly in the left lobe, revealed several distinctive signs of thyroid malignancy, such as microcalcifications and heterogeneous echo texture. The ultrasonographic findings of microcalcifications, which were compatible with the psammoma body on the histological analysis (Figure 2), are one of the most specific signs of thyroid malignancy, particularly in PTC [11]. Therefore, we performed ultrasound-guided FNA, and cytological investigation revealed the diagnosis of PTC. She underwent total thyroidectomy, and histopathology of thyroidectomy specimens confirmed the cytological diagnosis with nodal metastases.

There have been several other reports of thyroid malignancies in an AHTN, and the estimated cancer risk in hot nodules ranges from 3.1-11% [5,15-22]. To the best of our knowledge, 77 cases of thyroid malignancy related to AHTN or thyrotoxicosis have been reported [5]. The mean nodule size in these patients was 4.13 ± 1.68 cm. The patient in our case report had no high-risk history, and the maximum dimension of the nodule was 0.9 cm. If we had used the ≥1.0-1.5 cm size criteria for suspicious nodules that is recommended by ATA guidelines [4], our patient would not have been diagnosed with PTC. Therefore, before deciding whether AHTN is benign, we suggest that thyroid US should be performed by an experienced radiologist in all patients with hot nodules. If the radiologist reports any suspicious findings that suggest thyroid malignancy, as seen in the present case, the patient should be referred for FNA.

In conclusion, in contrast to the guidelines published by major endocrine societies, AHTN does not exclude thyroid malignancy. To exclude the possibility of thyroid cancer, thyroid US should be performed in all patients with AHTN. If the radiologist reports any suspicious findings that suggest thyroid malignancy, all patients should be referred for FNA and cytological evaluation. Our case gives further support for the recommendation that surgery should be performed more frequently to treat thyroid nodules (both cold and hot) in children and adolescents because of the lower prevalence of thyroid nodules and the higher malignancy rate in this age group.
References

1. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, et al. (2010) AACE/AME/ETA Task Force on Thyroid Nodules: American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocr Pract; 16:1-43.

2. Pacini F, Schlumberger M, Drahle H, Elisei R, Smit JW, et al. (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 154:787-805.

3. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, et al. (2005) Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 237:794-800.

4. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Thyroid 19:1167-1214.

5. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigman JM (2013) A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. Thyroid Res 6:7.

6. Paul SJ, Sisson JC (1990) Thyrotoxicosis caused by thyroid cancer. Endocrinol Metab Clin North Am 19:593-612.

7. Niedziela M (2006) Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer 13:427-453.

8. Corrias A, Einaudì S, Chioroboli E, Weber G, Crin A A, et al. (2001) Accuracy of fine needle aspiration biopsy of thyroid nodules in detecting malignancy in childhood: comparison with conventional clinical, laboratory, and imaging approaches. J Clin Endocrinol Metab; 86:4644-4648.

9. Dincau CA, Breuer C, Rikvées SA (2008) Differentiated thyroid cancer in children: diagnosis and management. Curr Opin Oncol 20:59-65.

10. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, et al. (2002) Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 87:1941-1946.

11. Iannuccilli JD, Cronan JJ, Monchik JM (2004) Risk for malignancy of thyroid nodules as assessed by sonographic criteria: the need for biopsy. J Ultrasound Med 23:1455-1464.

12. Cappelli C, Castellano M, Pirola I, Cumetti D, Agosti B, et al. (2007) The predictive value of ultrasound findings in the management of thyroid nodules. QJM 100:29-35.

13. Zimmerman D, LeTF AN (1998) Thyrotoxicosis in children. Endocrinol Metab Clin North Am 27:109-126.

14. Ciarrallo A, Makis W, Novales-Diaz JA (2011) Incidental papillary thyroid carcinoma in a patient presenting with Graves hyperthyroidism and concomitant obstructive sequestered intrathoracic multinodular goiter. Clin Nucl Med 36:145-147.

15. Lee ES, Kim JH, Na DG, Paeng JC, Min HS, et al. (2013) Hyperfunction thyroid nodules: their risk for becoming or being associated with thyroid cancers. Korean J Radiol 14:643-652.

16. Majima T, Doi K, Komatsu Y, Itoh H, Fukao A, et al. (2005) Papillary thyroid carcinoma without metastases manifesting as an autonomously functioning thyroid nodule. Endocr J 52:309-316.

17. Tufayli HM, Teot LA, Indyk JA, Witchell SF (2010) Papillary thyroid carcinoma in an autonomous hyperfunctioning thyroid nodule: case report and review of the literature. Thyroid 20:1029-1032.

18. Iwata M, Kasagi K, Hatabu H, Misaki T, Iida Y, et al. (2002) Causes of appearance of scintigraphic hot areas on thyroid scintigraphy analyzed with clinical features and comparative ultrasonographic findings. Ann Nucl Med; 16:279-287.

19. David E, Rosen IB, Bain J, James J, Kirsh JC (1995) Management of the hot thyroid nodule. Am J Surg 170:481-483.

20. Pazaitou-Panayiotou K1, Michalakis K, Paschke R (2012) Thyroid cancer in patients with hyperthyroidism. Horm Metab Res 44:255-262.

21. Croom RD 3rd, Thomas CG Jr, Reddick RL, Tawil MT (1987) Autonomously functioning thyroid nodules in childhood and adolescence. Surgery 102:1101-1108.

22. Niedziela M, Trejster E, Korman E (2002) Hot nodules in children and adolescents in western Poland from 1996 to 2000: clinical analysis of 31 patients. J Pediatr Endocrinol Metab 15:823-830.