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Case Report

Papillary thyroid carcinoma presenting as a functioning thyroid nodule: report of 2 rare cases

Liang Hu, Yijun Wu

Department of Thyroid Surgery, The First Hospital Affiliated to Zhejiang University, School of Medicine, No. 79 Qingchun Road, Hangzhou 310000, P. R. China

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Abstract: Introduction: Autonomously functioning thyroid nodules (AFTNs) are generally benign, whereas papillary thyroid carcinomas (PTCs) are mostly non-functioning. Graves' disease (GD) is the most common cause of hyperthyroidism (HD), followed by hyperfunctional adenoma or Plummer's disease. GD with AFTNs is called Marine-Lenhart syndrome, a relatively rare syndrome. In clinical practice, the presence of HD, AFTNs and PTC at the same time is extremely rare. Case presentation: Case 1: A 55-year-old middle-aged woman with a preoperative diagnosis of GD and HD with right AFTNs. Case 2: A 43-year-old middle-aged woman with a preoperative diagnosis of non-GD and HD with right AFTNs and right PTC. Case 1: Histology showed a 4 cm adenoma with a 1.0 cm PTC in the right lobe and a 0.3 cm PTC in the left lobe. The rest of the thyroid showed typical pathologic GD changes. The postoperative diagnosis was atypical Marine-Lenhart syndrome with bilateral PTC. Case 2: Histology showed a 0.4 cm PTC surrounded by nodular goiter. The postoperative diagnosis was toxic nodular goiter with PTC. Conclusion: This paper covers the relationships among PTC, HD and AFTNs, explains some common and uncommon clinical diagnoses, and reports two rare cases with these three diagnoses. Our ultimate purpose is to remind doctors that when handling nodules or HD, PTC as a diagnosis cannot be excluded. Instead, it is better to perform total or near-total thyroidectomy and intraoperative frozen biopsy or preoperative biopsy examinations to avoid omitting PTC, which needs reoperation.

Keywords: Hyperthyroidism, functioning nodule, thyroid carcinoma, PTC, Marine-Lenhart syndrome

Introduction

The most common pathologic diagnoses of autonomously functioning thyroid nodules (AFTNs) are hyperthyroid adenoma and toxic nodular goiter, while the clinical diagnoses of hyperthyroidism (HD) are Graves' disease (GD) and Plummer's disease [1, 2]. In HD, thyroid hormone is overproduced by the thyroid gland itself, leading to digestive effects, such as hypermetabolism and nerve excitability, as the main symptoms of this set of clinical syndromes [3]. More than 80% of clinical hyperthyroidism cases are considered GD, and GD is a thyroid autoimmune disease. AFTNs have been found by isotope scanning, and thyroid nodules absorb more radioactive enhancement than the surrounding thyroid tissue. Imaging-based diagnosis of nodules is usually more common for functioning nodules, and functioning nodules are usually benign [4]. Papillary thyroid carcinoma (PTC) is one of the most common malignant thyroid tumors; it is a differentiated thyroid cancer that accounts for approximately 80-90% of all thyroid cancers, and was first diagnosed by Hedinger and Sobin in 1974 [5]. Although the co-occurrence of clinical hyperthyroidism with cancer is also common, it is rare for the same nodule to be both functioning and malignant. This paper reports two rare clinical cases with these characteristics but different final diagnoses.

Case presentation

Case 1: A 55-year-old woman presented with a cervical mass, hyperactive mood, and trembling hands. The patient was a farmer in good health. Family history was negative for thyroid diseases. She had a palpable right thyroid nodule. Thyroid function tests showed suppressed thyroid stimulating hormone (TSH) (<0.004 mIU/L) but above-normal levels of thyroxine (227.6 nmol/L; normal range 62.68-150.84), triiodothyronine (4.61 nmol/L; normal range 0.89-2.44), and thyrotropin receptor anti-

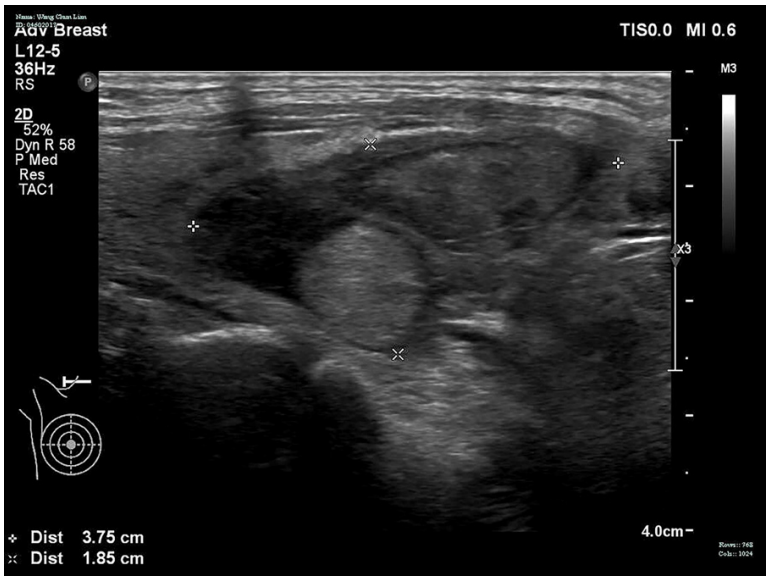


Figure 1. Thyroid ultrasound image revealing a 3.8 cm nodule in the right lobe.

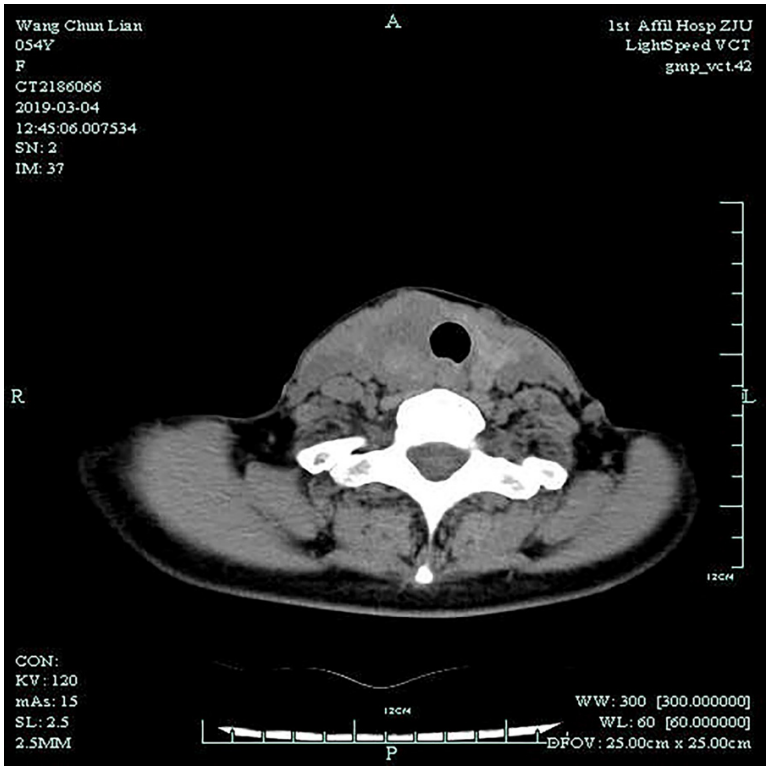


Figure 2. Thyroid CT image revealing a 3.8 cm nodule in the right lobe.

bodies (TRAb) (14.42 IU/L; normal range 0.00-1.75). Ultrasound and CT imaging revealed a right lobe nodule that was 3.8*1.9 cm in size with an unusual shape and classified as Thyroid Imaging Reporting and Data System (TI-RADS) 5 (**Figures 1** and **2**). 99mTc thyroid scintigraphy showed a suspicious hyperfunctioning nodule with suppression of the remainder of the parenchyma (**Figure 3**). Fine-needle aspiration cytology was not performed. A total thyroidectomy was performed. Case 2: A 43-year-old woman presented with a cervical mass. The patient was a worker in good health. Family history was negative for thyroid diseases. There were no noticeable positive signs. Thyroid function tests showed suppressed TSH (<0.01 mIU/L), above-normal levels of thyroxine (250.7 nmol/L; normal range 62.68-150.84) and triiodothyronine (5.21 nmol/L; normal range 0.89-2.44), and normal levels of TRAb (0.3 IU/L; normal range 0.00-1.75). Ultrasound imaging revealed a right lobe nodule 0.4 cm in size that was classified as TI-RADS 3-4a (**Figure 4**). Fine-needle aspiration cytology revealed PTC (**Figure 5**). 99mTc thyroid scintigraphy showed a right hyperfunctioning nodule with suppression of the remainder of the parenchyma (**Figure 6**). Right hemithyroidectomy was performed. Case 1: Histology showed a 4 cm adenoma nodule with a 1.0 cm papillary thyroid carcinoma tumour in the right lobe and a 0.3 cm PTC in the left lobe; the rest of the thyroid showed typical pathologic changes of GD (**Figure 7**). Case 2: Histology showed a 0.4 cm nodule with a papillary carcinoma surrounded by nodular goiter (**Figure 8**).

Discussion

Hyperthyroidism, functioning nodules and thyroid papillary carcinoma are clinical diagnoses that are defined from different angles (**Figure**

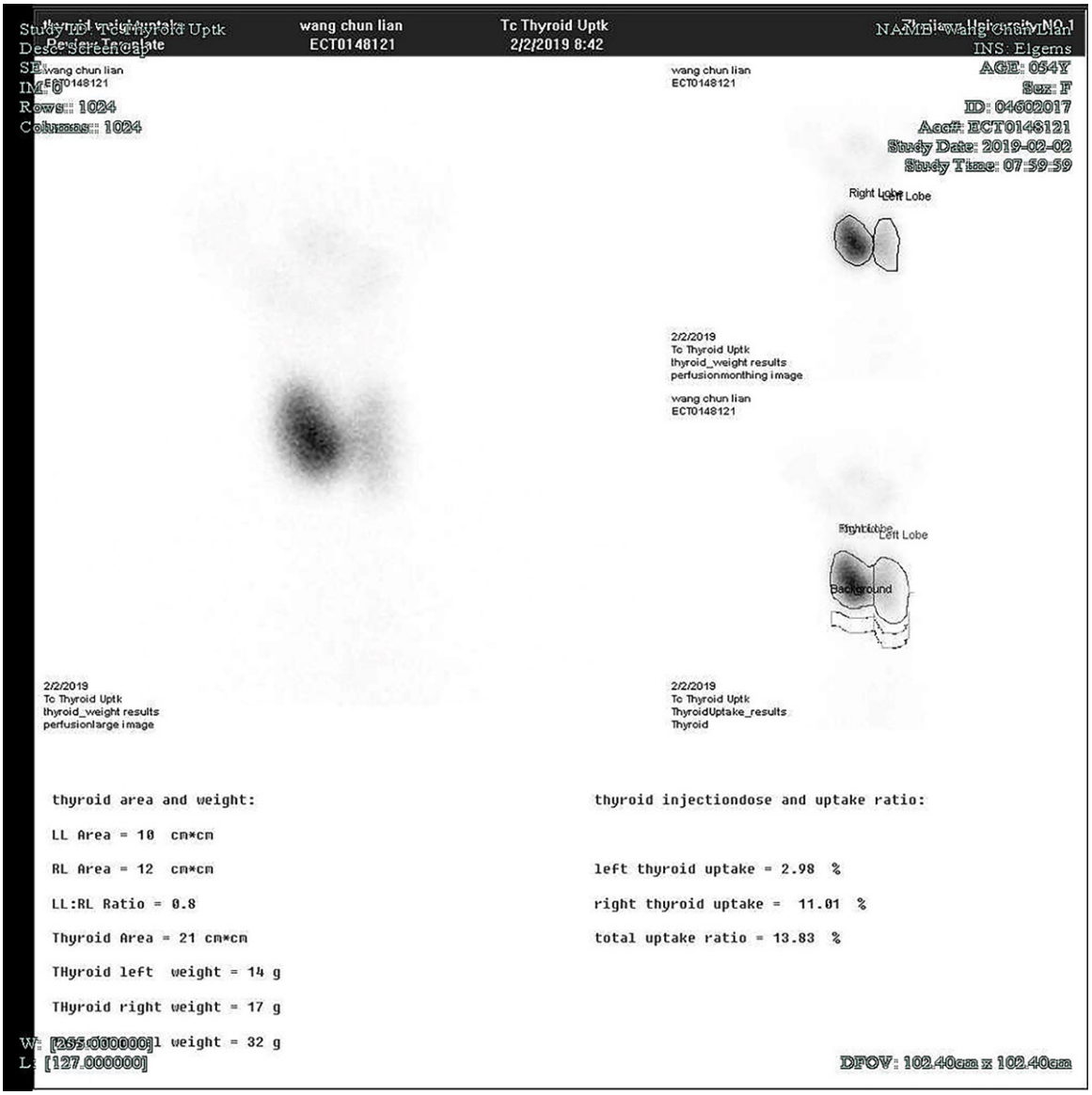


Figure 3. 99mTc thyroid scintigraphy image showing a right hyperfunctioning nodule and suppression of the remainder of the parenchyma.

9). In clinical practice, the presence of HD, AFTNs, and PTC at the same time is extremely rare. The most common of the above types is Graves' hyperthyroidism complicated by papillary carcinoma. Currently, the etiology of Graves' hyperthyroidism accompanied by malignant tumours (including PTC) is believed to be as follows [6, 7]: (1) the coexistence of GD and nonfunctional thyroid cancer; (2) the coexistence of GD and functional thyroid cancer; (3) the coexistence of toxic thyroid adenoma and nonfunctional thyroid cancer; (4) undifferentiated thyroid cancer destroys normal thyroid tissue and induces hyperthyroidism; (5) distant metastasis of thyroid cancer that produces excessive thyroid hormone; and (6) hyperfunctional thyroid cancer, in which hyperactive tissue is consistent with cancer tissue.

GD is a type of hyperthyroidism caused by an antibody to TRAb. Approximately 10%-31% of GD patients have thyroid nodules, most (>95%) of which are nonfunctional, and only a few present as functioning nodules. GD is associated with functioning nodules and causes hyperthyroidism, which is called Marine-Lenhart syndrome [8], as exemplified in case 1. 99mTc thyroid scintigraphy of Marine-Lenhart syndrome

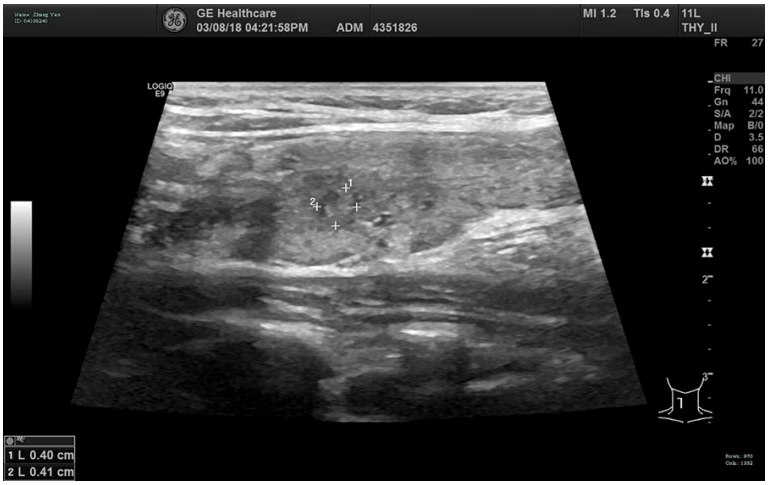


Figure 4. Thyroid ultrasound image revealing a 0.4 cm nodule in the right lobe.

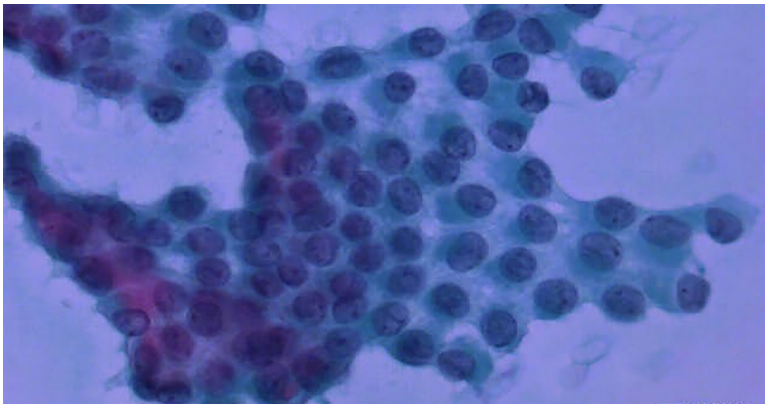


Figure 5. FNA cytologic image showing a malignant neoplasm with a follicular pattern and cytologic features of papillary carcinoma.

to the thyroid nodule as TSH-dependent, some nodules function independently of TSH, namely, those with low TSH; these functioning nodules are considered "hot" nodules by thyroid imaging. Some scholars summarized Marine-Lenhart syndrome as GD combined with Plummer's disease. In this article, the patient from case 1 had hyperthyroidism disease, and the TSH level was low, but the functioning nodules were hot nodules according to thyroid nuclide imaging [12, 13]. Other surrounding thyroid tissues remained concentrated, with elevated TRAb in the blood test and typical Graves' pathological microscopic characteristics (**Figure 4**) belonging to the category of atypical Marine-Lenhart syndrome. In case 2, although there was hyperthyroidism with functioning nodules, the blood test was negative for TRAb, and histology showed no characteristic microscopic changes of GD, so it could not be diagnosed as atypical Marine-Lenhart syndrome.

is distinctly different from that of common AFTNs and HD (**Figure 10**).

In 1911 and 1913, Marine and Lenhart reported GD complicated by functioning nodules for the first time [9, 10]. In 1972, Charkes found that 10 of 375 GD patients also had functioning nodules, which was called Marine-Lenhart syndrome. In 1992, Chandramouly et al. summarized the diagnostic criteria of this typical syndrome as follows [11]. Thyroid imaging suggested an enlarged thyroid with one or two non-functioning nodules; the nodules were TSH-dependent, while the surrounding tissues were not. After endogenous or exogenous TSH stimulation, the nodules became functional. The pathologic type was benign, so the thyroid nodule typical of Marine-Lenhart syndrome appeared when TSH was elevated. Rather than typical Marine-Lenhart syndrome, which refers

Case 1 reported in this paper is atypical Marine-Lenhart syndrome with PTC, which is extremely rare. According to a literature review, only one case was reported by Scherer et al. in 2013 [1]. The pathogenesis is not clear, but it is speculated that there are several possibilities as follows: (1) Cancer and high functional organization (focal adenoma or GD) occur in the same glands but at different locations (in the case of relatively common) [14-18]. (2) A greater tuberosity including multiple components but internal heterogeneity of different groups is observed [19-22]. (3) Cancer is a highly functional organization package around or close to the lesion [7, 10]. (4) Real high-functioning nodules and carcinoma tissue have the same organization [23, 24].

In a paper published by Mizukami et al. [4], twelve percent of thyroid cancer patients had

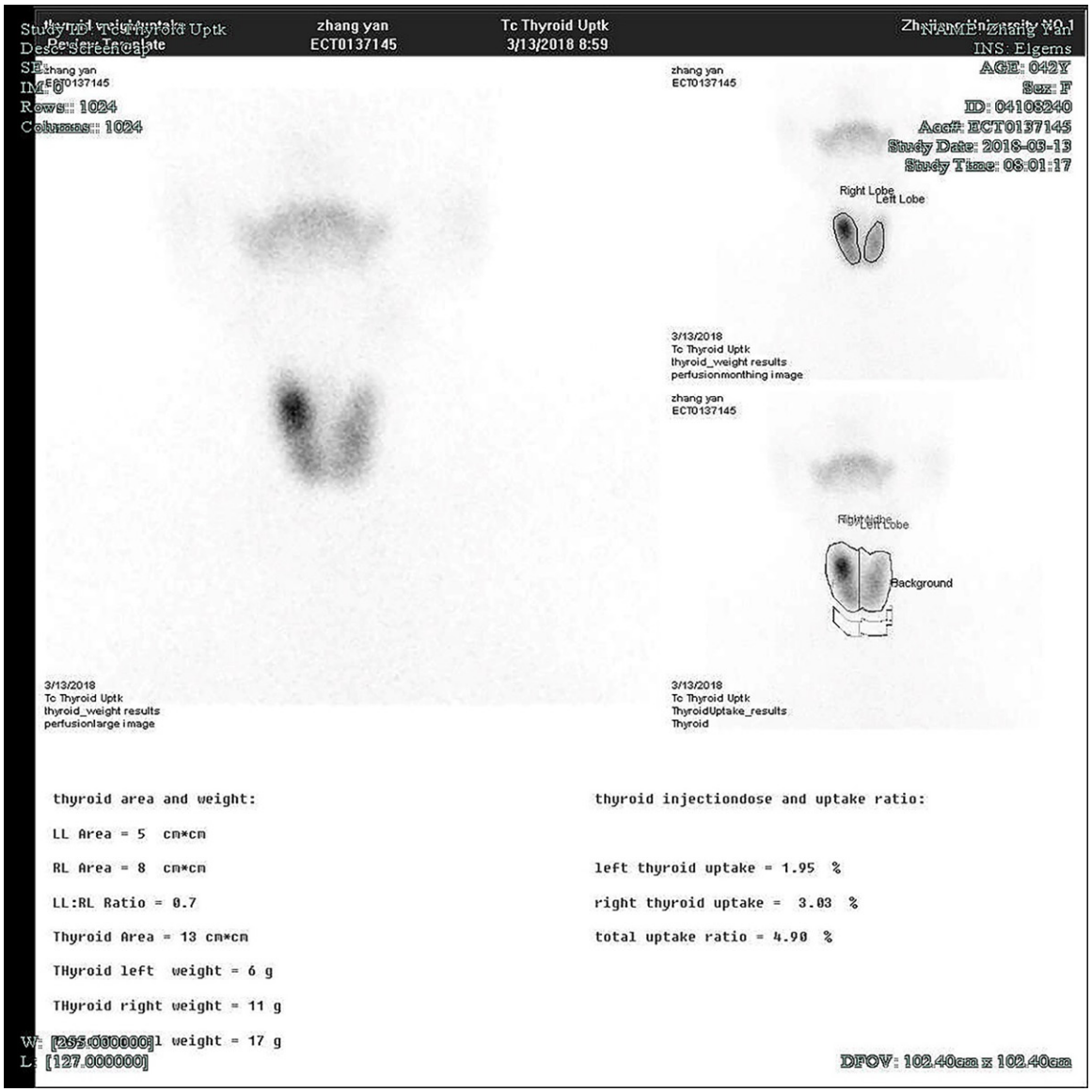
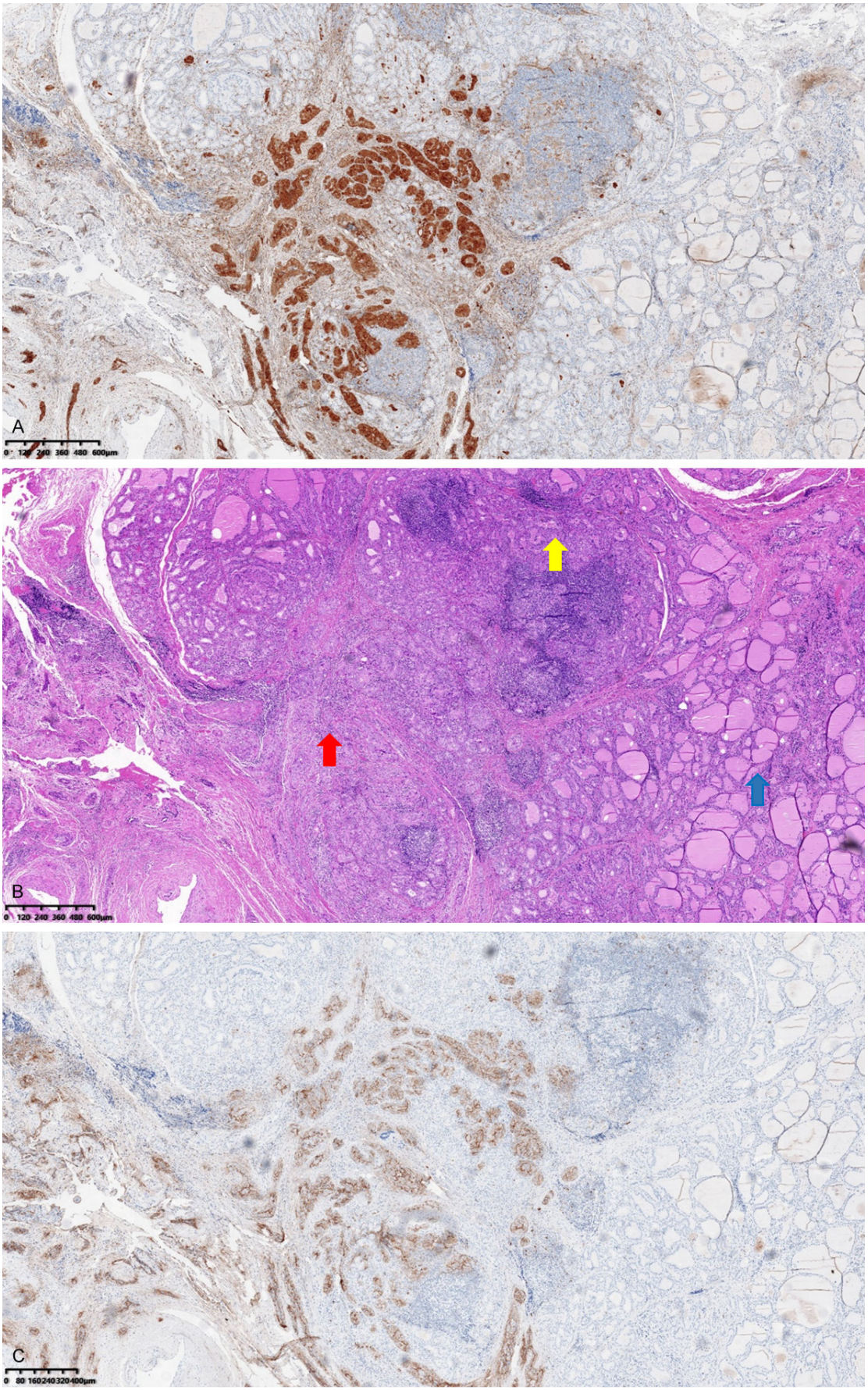


Figure 6. 99mTc thyroid scintigraphy image showing a right hyperfunctioning nodule and suppression of the remainder of the parenchyma.

autonomic nodules. A retrospective study of 31 cases suggested a relationship between the incidence of malignancy and the uptake of radioactive drugs in the remainder of the gland. Of the 17 cases in which radioactive uptake were completely inhibited by thyroid nodules, only 1 was malignant, with an incidence of 5.9% [25, 26]. On the other hand, in the remaining 14 cases, a significant amount of radionuclides was absorbed into the glandular parenchyma outside the nodule, and the incidence of cancer was significantly higher than that in cases with little uptake (57.1%). Therefore, in our case 1, an atypical Marine-Lenhart syndrome patient, ECT examination revealed radionuclide development in areas other than functioning nodules, which was not a typical image characteristic of toxic adenoma, and postoperative pathologic results also showed multifocal papillary carcinoma, consistent with the results of this study.

In most cases, the tumors are small, single-focus cancers with multiple foci [27, 28], and follicular or Hurthle cells [29] have also been reported. Nishikubo described a 22-year-old woman with multifocal thyroid cancer who had hyperthyroidism [29]. The radionuclide scan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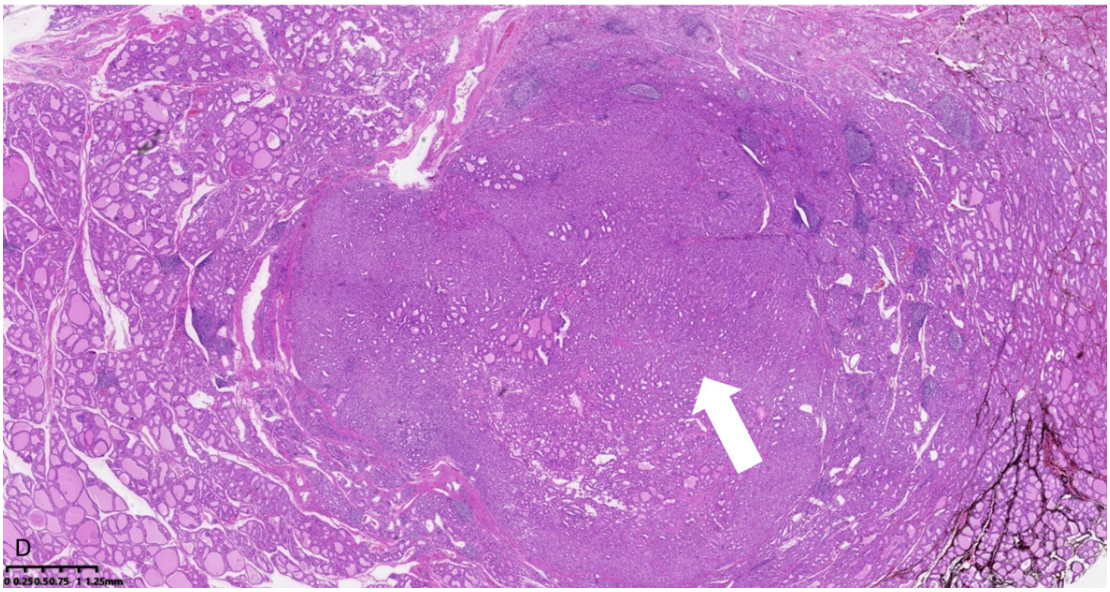


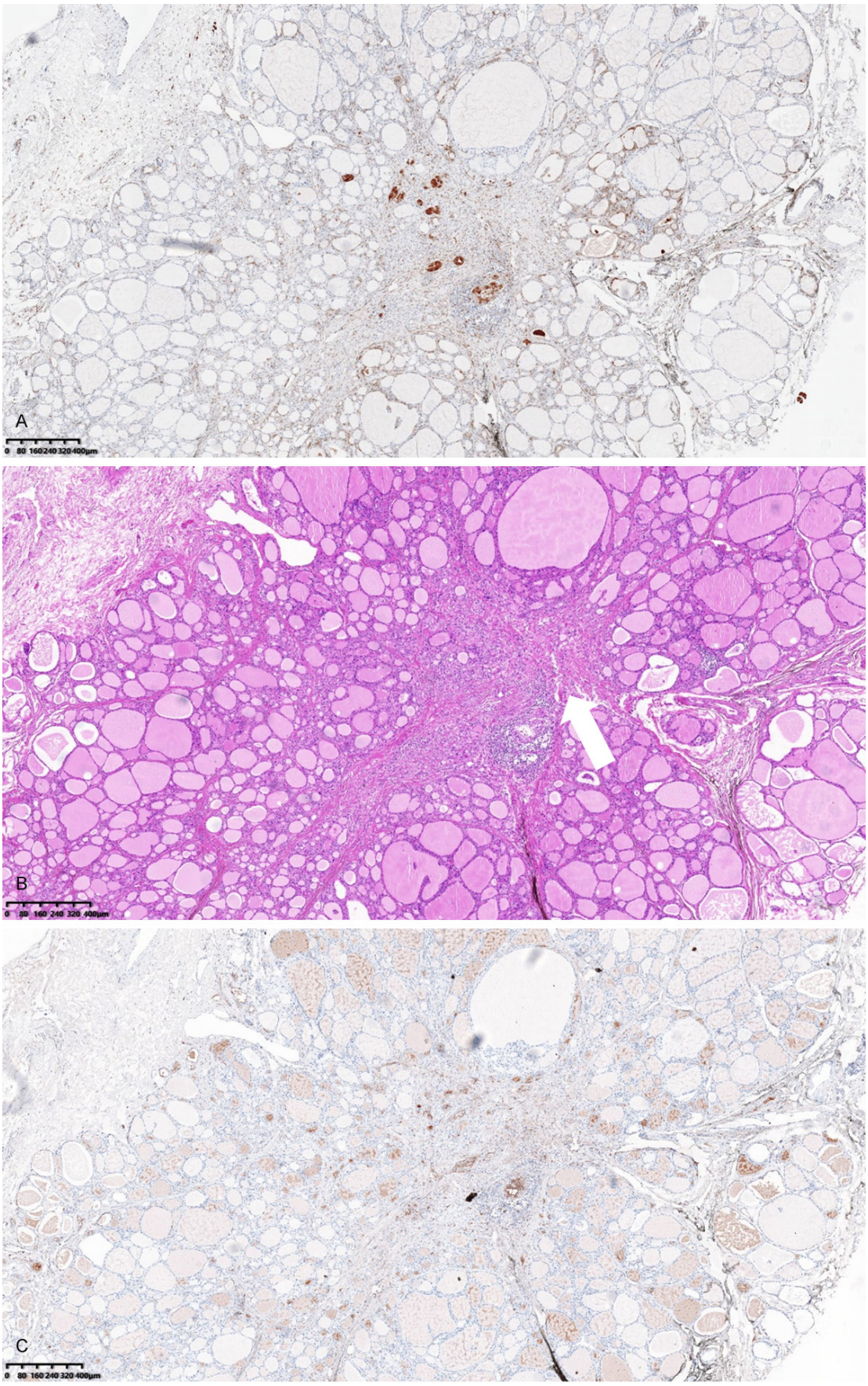
Figure 7. A. Galectin-3 immunohistochemical staining was positive, indicating the papillary carcinoma component. B. H&E staining; papillary carcinoma (red arrow), adenoma (yellow arrow) and GD (blue arrow) coexist. C. Meso cell immunohistochemical staining was positive, indicating the papillary carcinoma component. D. Typical coexistence of adenomas and GD; the arrow indicates the characteristic structure of an adenoma.

showed high iodine absorption in both lobes. Subtotal thyroidectomy was performed 45 days after antithyroid therapy. The pathological diagnosis was follicular carcinoma and PTC with multiple lesions in both lobes. In a retrospective study of 941 patients [30, 31], there was no significant difference in the incidence of malignancy between hot and cold nodules. This study suggests that the routine use of radionuclide scans in the diagnosis and treatment of thyroid nodules is not useful in screening for malignancies since high-functioning nodules may be associated with thyroid cancer or thyroid cancer may coexist outside the high-functioning nodules.

The pathophysiologic reasons for the coexistence of HD and cancer are debatable. Traditionally, malignant tumours are believed to be more likely to occur in patients with elevated TSH because TSH promotes tumor growth [32]. Some scholars believe that the cause of HD or GD may also cause tumour transformation [33]. Although TRAb plays a central role in the pathogenesis of GD, the significance of these antibodies in the pathogenesis of thyroid cancer remains unclear [34].

Cantalamessa et al. found no significant relationship between TRAb concentration and nodules in their patients [23]. Mutations in the activation of the TSH receptor (TSHR) gene are associated with HD. In rare cases, activation of TSHR mutations has been observed in patients with AFTNs and thyroid cancer [35]. In thyroid nodules containing papillary carcinoma from an 11-year-old girl with HD who was TRAb negative [17], the researchers found a missense mutation, M453T, resulting from the TSHR mutation of the somatic heterozygote. Somatic mutations of the TSHR and G protein a chain (Gsa) genes have also been frequently reported in high-functioning adenoma and cancer-free Plummer's disease [20, 21].

Whether there is a further relationship between TSHR and thyroid cancer is unconfirmed, but it is currently believed that TSHR generates biological effects mainly by combining with TSH [36]. TSHR is mainly expressed on the surface of thyroid follicular epithelial cells and plays a biologic role in regulating the growth of thyroid cells and the synthesis and secretion of thyroid hormones [37]. Since the TSHR gene was cloned, it has been a research hotspot [38]. To date, more than 20 pathogenic mutations of the TSHR gene have been identified, all of which are missense mutations, with 97.4% of the mutations occurring in the 10th exon [39].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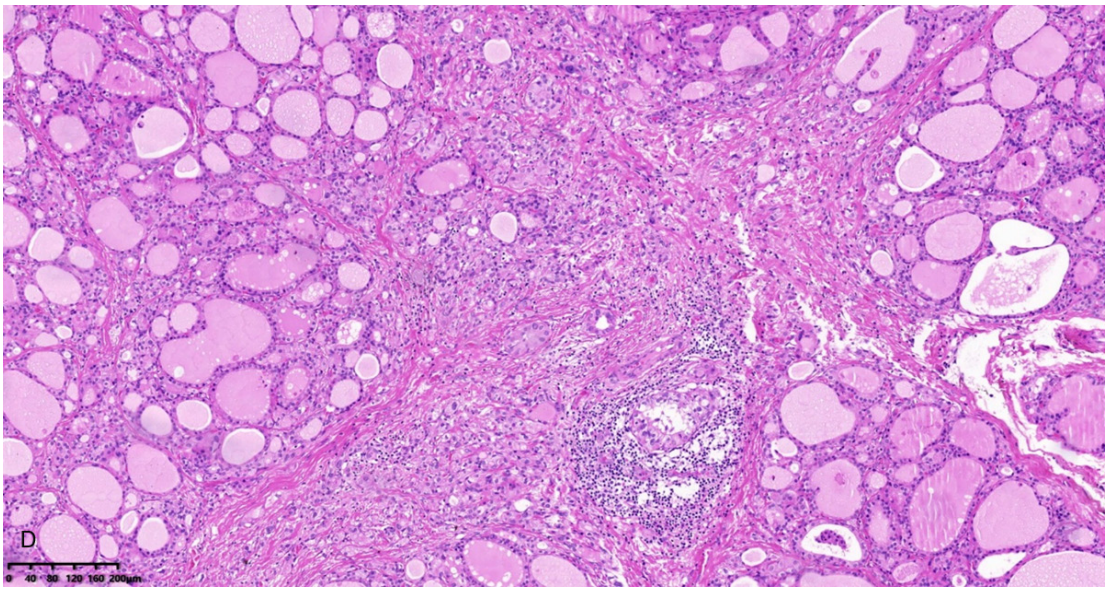

Figure 8. A. Immunohistochemical staining of galectin-3 was positive in the papillary carcinoma component. B. Positive H&E staining of the papillary carcinoma (arrow) and nodular goiter. C. Immunohistochemical staining of meso cells was positive in the papillary carcinoma component. D. At high magnification, papillary carcinoma and nodular goiter coexisted.

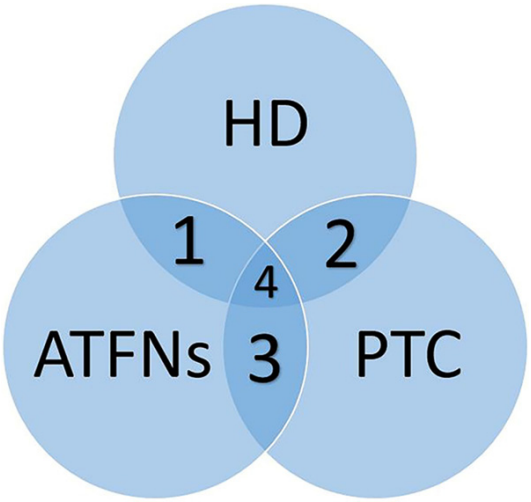

Figure 9. Diagram of the relationships between these definitions: ① Marine-Lenhart syndrome, [1] FTC with AFTNs, [53] ② GD with PTC, ③ Euthyroid GD with PTC, [49] and ④ ATFNs with PTC, Plummer's disease with PTC (case 2), hyperfunctioning PTC, [35] Marine-Lenhart syndrome with PTC (case 1).

TSHR mutations have been reported in DTC in many studies [17, 35]. However, the hyperfunctional thyroid cancer reported by Bourasseau et al. [40, 41] had no TSHR and Gsa gene mutations, suggesting the possibility of other gene damage. Unfortunately, in our two cases, we did not conduct further genetic testing for TSHR. Therefore, the incidence and significance of TSHR gene mutations in hyperthyroidism with thyroid cancer remain unclear, and further studies are needed to clarify this issue.

In 1992, Michigishi et al. [42]. reported a case of thyroid cancer caused by AFTNs with normal thyroid function, which is extremely rare because in most cases, functioning nodules can cause HD, so this disease is also called euthyroid GD. A retrospective study of 296 Turkish adults with AFTNs showed a malignancy incidence of only 0.34%, with an average age of 54.9 ± 12.4 years [43]. However, some cases have been reported describing hyperactive nodules found in thyroid cancer [28, 44]. A Japanese study reported that of 17 AFTN patients aged 13-68, 2 were diagnosed with thyroid cancer (1 follicular papillary cancer and 1 follicular cancer). Both children in this study had AFTNs [4]. The size of AFTNs was not correlated with thyroid function. Among American children with AFTNs, 6/53 (11.3%) were diagnosed with highly differentiated thyroid cancer [27]. Although the detection of thyroid cancer in AFTNs is uncommon, these reports support our recommendation that AFTNs should be fully assessed in all age groups, including children, with FNAB as necessary. If surgery is performed, adenolobectomy or subtotal resection

Figure 10. ECTs from the two cases were compared with ECTs for common AFTNs and HD cases.

is the best option, and it is also best to freeze samples for pathological examination during the operation to avoid the omission of thyroid papillary cancer and other malignant tumors.

Acknowledgements

Written informed consent was obtained from the patient for publication of this case report andany accompanying images.

Disclosure of conflict of interest

None.

Abbreviations

AFTNs, autonomously functioning thyroid nodules; HD, hyperthyroidism; GD, Graves' disease; PTC, papillary thyroid carcinoma; TSH, thyroid stimulating hormone; TRAb, thyrotropin receptor antibodies; TI-RADS, Thyroid Imaging Reporting and Data System.

Address correspondence to: Dr. Liang Hu, Department of Thyroid Surgery, The First Hospital Affiliated to Zhejiang University, School of Medicine, No. 79 Qingchun Road, Hangzhou 310000, P. R. China. Tel: +86-13758154102; E-mail: hlzjxs@zju.edu.cn

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