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Original Article

Papillary thyroid carcinoma in a hyperfunctioning autonomous nodule : A diagnostic paradox challenging clinical guidelines

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Abstract

Background: Papillary thyroid carcinoma (PTC) is rarely found within hyperfunctioning (hot) thyroid nodules, which are typically considered benign. This case challenges the prevailing notion that functional autonomy excludes malignancy and underscores the need for a nuanced diagnostic approach.

Methods: We report the case of a 63-year-old woman with clinical hyperthyroidism and a palpable right thyroid nodule. Biochemical tests confirmed thyrotoxicosis (TSH <0.005 µIU/mL, free T4 25.55 pmol/L and T3 7.69 pmol/L). Despite the hyperfunctioning profile, thyroid ultrasound showed high-risk features, including hypoechogenicity, microcalcifications, irregular margins, and elevated stiffness on shear wave elastography, classifying the lesion as ACR-TIRADS 5. A 99mTc scan confirmed a hyperfunctioning nodule. Fine-needle aspiration cytology (FNAC) revealed PTC. She subsequently underwent total thyroidectomy.

Results: FNAC revealed PTC. Histopathology confirmed a 13 mm intrathyroidal papillary carcinoma with mixed classic (40%) and oncocytic (60%) subtypes, without capsular or extrathyroidal extension. The background thyroid tissue showed macrofollicular hyperplasia. The patient recovered uneventfully and did not require radioactive iodine ablation. Genetic testing was unavailable.

Conclusion: This case illustrates that malignancy can coexist with hyperfunctioning thyroid nodules. Suspicious sonographic features should not be dismissed due to functional status. Cytological evaluation remains essential when ultrasound findings raise concern, supporting a shift toward integrated diagnostic decision-making in thyroid nodule assessment.

Key words: Thyroid neoplasms, Thyroid nodule, Hyperthyroidism, Papillary thyroid cancer, Radionuclide imaging, Ultrasonograph

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Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the endocrine system, accounting for approximately 80%–85% of differentiated thyroid cancers (1). Its incidence has increased markedly in recent decades, particularly among women and young adults, with a female-to-male ratio approaching 3:1 (2,3). In contrast, autonomously functioning thyroid nodules (AFTNs)-characterized by suppressed thyroid-stimulating hormone (TSH) and increased radionuclide uptake on scintigraphy-constitute a minority of thyroid nodular lesions and are typically associated with benign, hormone-producing adenomas (1,4). This functional profile has traditionally led to their exclusion from invasive diagnostic procedures, such as fine-needle aspiration biopsy (FNAB), under the assumption that they are of low oncologic relevance. However, over the past decade, isolated cases of PTC arising within AFTNs have been reported, challenging this long-standing paradigm. Several publications have described patients with hyperfunctioning nodules that were subsequently found to harbor malignant histopathological features.

Despite these observations, the pathophysiological mechanisms that allow the coexistence of functional autonomy and malignant transformation remain poorly understood. Activating mutations, such as BRAF V600E or alterations in the TSH receptor, have been proposed as possible contributors, though the current evidence is limited and inconclusive (4, 5). Moreover, no standardized clinical criteria exist to guide the decision-making process regarding surgery or biopsy in such cases, particularly when imaging findings are atypical or discordant (3, 4, 6, 7). This case, therefore, offers clinical and academic relevance by illustrating a rare presentation of PTC within an autonomously functioning thyroid nodule in a patient with clinical hyperthyroidism. Its importance lies in demonstrating how the application of high-risk ultrasound criteria-despite the nodule's functional status-facilitated timely intervention and accurate diagnosis.

Methods

This case report was conducted in accordance with ethical standards for clinical research. It received approval from the Institutional Research Ethics Committee of the Faculty of Medicine, Universidad Nacional de Trujillo, in accordance with national regulations and the Declaration of Helsinki. The approval code is Of. N° 111-2025-UNT-FM-C.E. Informed consent was obtained from the patient for publication of this case and accompanying images. Confidentiality and anonymity were guaranteed throughout the process.

Result

A 63-year-old female patient from Lima, Perú, with a medical history of hyperthyroidism, prediabetes, and osteoporosis, was found to have a thyroid nodule during routine medical surveillance. Physical examination revealed a mild goiter with irregular consistency and nodular predominance in the right lobe. Laboratory evaluation at presentation showed suppressed thyroid-stimulating hormone (TSH <0.005 µIU/mL; reference range: 0–4), elevated free thyroxine (FT4: 25.55 pmol/L; reference: 9–20), and elevated free triiodothyronine (FT3: 7.69 pmol/L; reference: 3.1–6.8), with negative thyroid autoantibodies.

Thyroid ultrasound demonstrated a solid, hypoechoic, subcapsular nodule with microcalcifications and indistinct margins (figure 1A), consistent with ACR-TIRADS category 5. Color Doppler imaging revealed mixed vascularity with central predominance and penetrating vessels (figure 1B). Shear wave elastography (SWE) indicated increased stiffness, measuring 140.2 kPa (figure 1C).

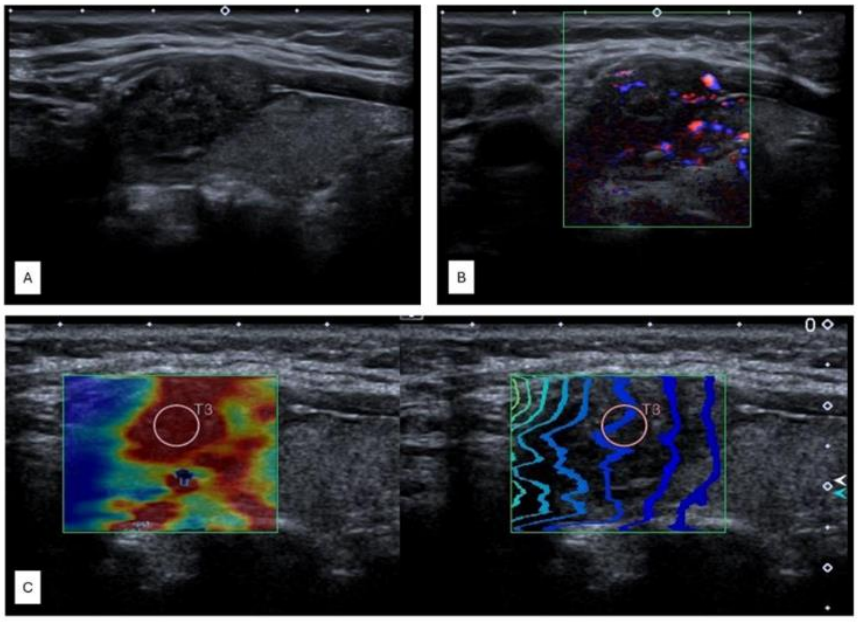

Figure 1. A) Thyroid ultrasound. B) Thyroid Color Doppler. C) Thyroid shear wave elastography.

A subsequent technetium-99m (Tc-99m) thyroid scan revealed a hyperfunctioning nodule in the right lobe, with partial suppression of the surrounding parenchyma, consistent with an autonomous nodule (figure 2). The overall thyroid uptake was 2.43%, within the normal range (0.3%–4.5%). Fine-needle aspiration cytology (FNAC) was then performed, and cytologic evaluation was diagnostic for PTC, Bethesda category VI

The patient underwent an extended total thyroidectomy, including resection of adjacent musculature.

Intraoperatively, a firm 2 cm nodule was identified in the upper portion of the right thyroid lobe. Histopathological examination confirmed the diagnosis of PTC, composed of 60% oncocytic and 40% classic subtypes, confined to a 13 mm nodule without capsular or extrathyroidal extension. The surrounding thyroid tissue demonstrated macrofollicular hyperplasia (figure 3). The tumor was staged as pT1b according to the TNM classification system.

The postoperative course was favorable. The patient did not receive radioactive iodine (I-131) ablation, and levothyroxine therapy was initiated for hormone replacement. Genetic analysis for TSH receptor mutations and PTC-associated oncogenic variants was not available. At present, the patient remains under outpatient endocrinology follow-up, with no clinical or biochemical evidence of disease recurrence

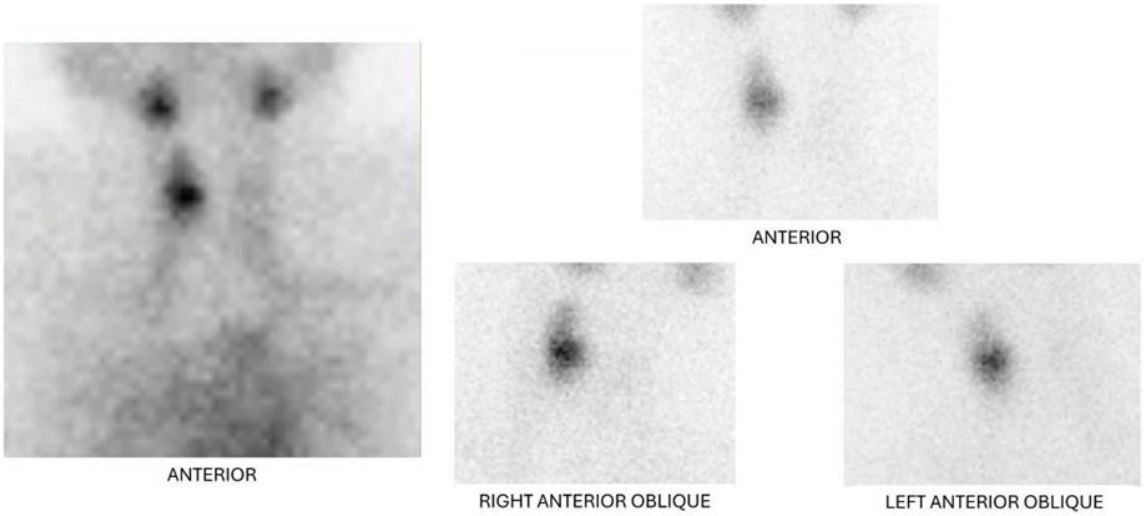

Figure 2. Thyroid scan with 99mTc

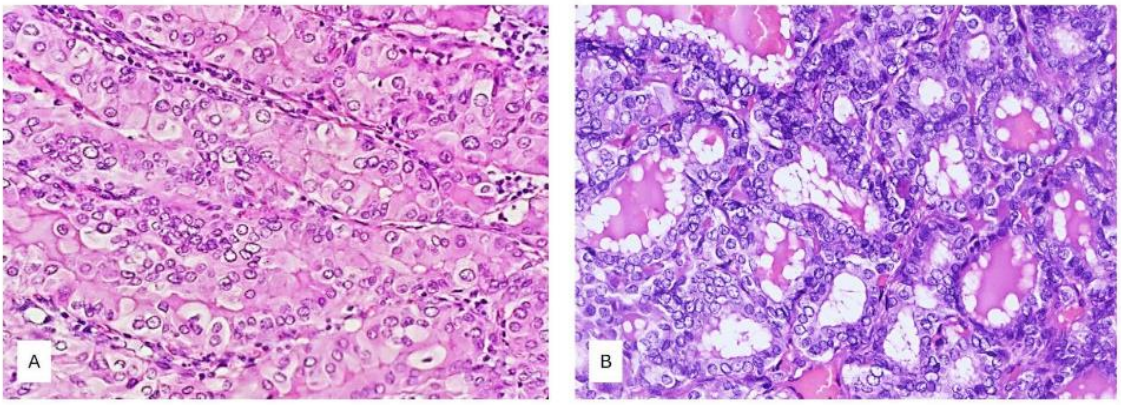

Figure 3. A) Papillary thyroid cancer oncocytic subtype. B) Papillary thyroid cancer classic subtype.

Discussion

Although autonomously functioning thyroid nodules (AFTNs) are generally regarded as benign lesions, recent evidence has challenged this assumption. While earlier studies estimated the malignancy rate in AFTNs to be less than 3%, more recent systematic reviews have documented up to 34 confirmed cases of PTC arising within AFTNs, including several in patients with apparently low clinical risk profiles (8–10). These findings reinforce the view that functional status alone should not be considered a definitive indicator of benignity at any age. Although the overall prevalence of malignancy in AFTNs remains low, the clinical implications are significant: relying exclusively on the functional profile of a nodule to rule out malignancy may result in delayed diagnosis and treatment (11).

Current clinical guidelines frequently state that fine-needle aspiration cytology (FNAC) is unnecessary in hyperfunctioning nodules due to their presumed low risk of malignancy. However, emerging data suggest the need for a more nuanced and individualized approach. Certain case

series have reported malignancy rates of up to 12.5% in toxic nodules—far exceeding the historically cited 3%-and multicenter surgical studies have documented cancer rates as high as 18.3% in patients with toxic nodular goiter undergoing thyroidectomy (11). The 2023 European Thyroid Association (ETA) guidelines continue to recommend against FNAC in nodules with increased radionuclide uptake unless high-risk features are present on ultrasound. Nonetheless, the guidelines acknowledge the ongoing controversy and emphasize that clinical judgment should prevail when discordant findings exist between imaging modalities (11-13). Notably, a unique case published in the European Thyroid Journal described a hyperfunctioning PTC harboring both a BRAF V600E mutation and a TSH receptor (TSHR) D727E polymorphism, challenging the traditional belief that oncogenic mutations are confined to non-functioning thyroid malignancies (14).These findings support the integration of additional diagnostic parameters-such as suspicious sonographic features and molecular alterations-alongside TSH suppression and scintigraphic uptake when evaluating the need for biopsy (15).In the present case, the patient was a 63-year-old woman. Although the literature indicates that most reported cases of PTC in AFTNs occur in women over the age of 50, this trend has not been systematically analyzed in existing reviews (3,8,9). Some studies suggest that the biological behavior of PTC may be more aggressive in postmenopausal women (1,9); however, no such aggressive features were observed in this patient.From a diagnostic standpoint, this case is particularly noteworthy due to the concordance between high-risk ultrasound features and the indication for FNAC, despite the nodule's hyperfunctioning status (9, 12). The sonographic findings-including marked hypoechogenicity, microcalcifications, irregular margins, and elevated stiffness on shear wave elastography (140.2 kPa)-fulfilled criteria for ACR-TIRADS 5 and justified further cytological evaluation. This individualized diagnostic approach is supported by multiple reports in the literature that advocate tailoring management based on patient-specific imaging and clinical features. For example, Pereira-Macedo et al. (8) described a 21 mm hyperfunctioning nodule with microcalcifications and TI-RADS 5 classification that underwent FNAC, confirming papillary thyroid carcinoma and leading to total thyroidectomy with clear margins and no evidence of capsular or vascular invasion.In our patient, although the nodule was smaller (13 mm), the presence of multiple high-risk sonographic features-including hypoechogenicity, microcalcifications, irregular borders, and high stiffness-similarly warranted FNAC. Histopathological analysis subsequently revealed a mixed papillary carcinoma composed of oncocytic (60%) and classic (40%) components. While this histologic profile deviates from the most commonly reported distribution, where the classic variant predominates in 71% of cases and the oncocytic variant in approximately 18% (8,12), it highlights the potential underrecognition of mixed histological subtypes in autonomously functioning nodules. This underscores the importance of not excluding malignancy solely on the basis of functional imaging findings and emphasizes the diagnostic value of morphological ultrasound features (15).

At the molecular level, it is important to note that mutations such as BRAF V600E-present in over 45% of PTC cases-and alterations in the TSH receptor have been identified in malignant functional thyroid tissue (5,14,16). These molecular events may help explain the rare coexistence of hormonal autonomy and neoplastic transformation. Unfortunately, molecular profiling was not available in the present case, limiting insights into the tumor's genetic drivers. Nevertheless, the absence of extrathyroidal extension, positive margins, or lymph node metastases, combined with a favorable postoperative course, supports a low-risk profile and justified the decision to forego radioactive iodine therapy (3,12).For patients with PTC larger than 1 cm, total thyroidectomy is generally the preferred surgical approach, especially in the presence of high-risk features such as suspicious ultrasound characteristics, extrathyroidal extension, or lymph node metastases. Lobectomy may be an acceptable alternative for tumors measuring 1–4 cm in the absence of such features (9,16,17). Regardless of the surgical extent, close postoperative surveillance is essential due to the risk of recurrence or disease persistence.

In cases where PTC arises within an autonomously functioning thyroid nodule, surgical management serves a dual purpose: treating both the malignancy and the hyperthyroid state. It also enables adjuvant radioactive iodine (RAI) therapy if indicated, depending on the patient's risk stratification. In the present case, however, RAI ablation was deemed unnecessary (12, 14). According to the 2022 Taiwan multicenter consensus, RAI may be omitted in low-risk PTC, even in cases with vascular invasion, lymph node metastases, or aggressive histologic subtypes, provided the tumor is ≤2 cm, intrathyroidal, and postoperative serum thyroglobulin is undetectable in the absence of anti-thyroglobulin antibodies (18). Our patient's favorable histopathologic profile-including a 13 mm intrathyroidal tumor without lymph node involvement, mixed classic/oncocytic histology, undetectable

postoperative thyroglobulin, and suppressed TSH-justified the decision to forgo adjuvant RAI in accordance with current international guidelines, minimizing the risk of overtreatment.In the broader context of low-risk PTC, either lobectomy or total thyroidectomy typically yields excellent long-term outcomes, with 10-year overall and disease-free survival rates exceeding 90%, disease-specific mortality under 5%, and low recurrence rates, as demonstrated in large cohort studies and recent systematic reviews (7). While the presence of an autonomous nodule does not significantly alter this prognosis, it may influence surgical planning, as autonomously functioning tissue tends to be RAI-resistant and may affect postoperative hormonal balance (10,12).This case challenges the traditional notion that autonomously functioning thyroid nodules are invariably benign, illustrating that papillary thyroid carcinoma can coexist with hyperfunction. Despite the nodule's "hot" status, high-risk ultrasound features justified biopsy and led to timely diagnosis. The tumor's mixed histology and favorable outcome without radioactive iodine further support individualized, risk-adapted management. This case highlights the importance of prioritizing sonographic findings over functional imaging in biopsy decisions.

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