



**Papillary Thyroid Carcinoma Revealed by a Toxic Nodule: A Case Report
and Literature Review**

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Abstract

Hyperfunctioning thyroid nodules are classically considered benign, leading to a generally reassuring diagnostic approach. However, recent studies suggest that the risk of malignancy, although low, is not negligible. We report a rare case of papillary thyroid carcinoma revealed within a toxic thyroid nodule and review the relevant literature to highlight diagnostic and therapeutic implications.

A 38-year-old woman presented with an anterior cervical swelling and respiratory discomfort. Biological assessment showed subclinical hyperthyroidism. Cervical ultrasound revealed a left lobar solid–cystic nodule classified EU-TIRADS 3, and 99mTc Pertechnetate Thyroid scintigraphy demonstrated a nearly total autonomous hyperfunctioning left-lobe nodule. Owing to compressive symptoms from a plunging goiter, total thyroidectomy was performed. Histopathological examination unexpectedly revealed a classic papillary thyroid carcinoma confined to the thyroid (pT2NxMx) with vascular emboli. The patient subsequently underwent radioactive iodine ablation with 3.7 GBq of I-131, followed by suppressive L-thyroxine therapy. Post-therapy whole-body scintigraphy showed only residual thyroid bed uptake, and follow-up demonstrated undetectable thyroglobulin levels with no evidence of recurrence.

This case illustrates that malignancy can occur in autonomously functioning thyroid nodules, even when ultrasound features suggest low to intermediate risk. It underscores the limitations of relying solely on hyperfunctionality or TIRADS classification to exclude cancer. An integrated approach combining clinical context, ultrasound, scintigraphy, and, when indicated, cytology is essential. Early recognition and appropriate management allow outcomes comparable to those of differentiated thyroid carcinoma diagnosed in euthyroid settings.

Keys words: *Papillary thyroid carcinoma; Toxic thyroid nodule, Radioactive iodine therapy.*

Introduction

A toxic thyroid nodule is a nodule that functions autonomously, causing excessive secretion of thyroid hormones. Hyperfunctioning thyroid nodules, also referred to as “hot nodules,” represent approximately 5% to 10% of all thyroid nodules. Classically, they are benign in nature, most often adenomatous (1).

The prevalence of their association with thyroid cancer ranges from 0.2% to 8.3% according to the most recent studies, calling into question the traditionally reassuring approach of international guidelines (2).

We report a case of a patient followed for hyperthyroidism who underwent a ^{99m}Tc Pertechnetate thyroid scintigraphy at the Nuclear Medicine Department of Hassan II University Hospital in Fez. The examination revealed the presence of a toxic nodule, and subsequent complementary investigations led to the diagnosis of papillary thyroid carcinoma.

Observation

This is a 38-year-old woman, G4P4, with no significant past medical history, with a reported but undocumented family history of thyroid disease in a cousin. She was referred to endocrinology for evaluation of an anterior cervical swelling associated with a sensation of respiratory discomfort. Clinical examination revealed a stage II nodular goiter, with a well-defined left lobar nodule on palpation, and no associated cervical lymphadenopathy. Hormonal assessment demonstrated subclinical hyperthyroidism, characterized by a suppressed TSHus at 0.081 $\mu\text{UI}/\text{mL}$ and a free T4 within normal limits (0.77 ng/mL), without use of synthetic antithyroid drugs. Cervical ultrasound showed an enlarged thyroid gland with a plunging morphology, containing a well-circumscribed left lobar solid-cystic nodule, iso-echogenic and heterogeneous, measuring 25 × 20 mm, classified EU-TIRADS 3. ^{99m}Tc Pertechnetate Thyroid scintigraphy for nodule characterization demonstrated a nearly total left lobar autonomous pre-toxic nodule (Figure 1). Given the compressive nature of the plunging goiter and the significant respiratory discomfort, surgical management was indicated. The patient underwent total thyroidectomy. Histopathological analysis with immunohistochemical studies confirmed a diagnosis of classic-type papillary thyroid carcinoma of the left lobe, classified pT2NxMx, confined to the thyroid, without capsular invasion, and with the presence of four vascular emboli (Figure 2). The patient was subsequently referred to nuclear medicine for isotopic management. Six weeks after surgery, a therapeutic dose of radioactive iodine was administered at 3.7 GBq in a radioprotected room, in compliance with radiation-safety protocols. The pre-therapy evaluation showed adequate thyroid-stimulating hormone elevation with TSHus >30 UI/mL, thyroglobulin at 10 ng/mL, and negative anti-thyroglobulin antibodies. Whole-body I-131 scintigraphy performed on the fifth day after radioactive iodine administration revealed a single focus of cervical uptake corresponding to a thyroid remnant, with no abnormal distant uptake. The

patient was subsequently placed on suppressive-dose L-thyroxine (2.4 $\mu\text{g}/\text{kg}/\text{day}$). Two follow-up evaluations showed negative tumor markers, with an undetectable thyroglobulin level (<0.1 ng/mL), as well as a postoperative cervical ultrasound demonstrating an empty thyroid bed without residual tissue or local recurrence.

Based on the combined morphological, functional, and biological findings, the patient was declared in complete remission. Lifelong L-thyroxine therapy was recommended to maintain TSH at an intermediate target level (intermediate recurrence risk), in accordance with the 2025 American Thyroid Association (ATA) guidelines. Ongoing surveillance is now performed annually and includes tumor-marker testing, supplemented by morphological evaluation when necessary.

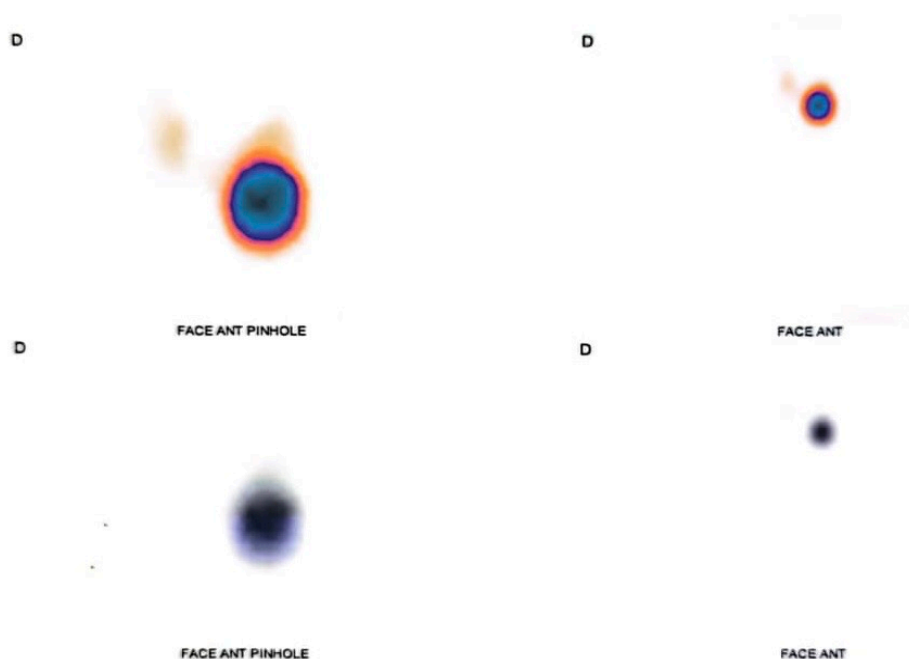


Figure 1: $^{99\text{m}}\text{Tc}$ Pertechnetate Thyroid image showing an area of near-complete hyper uptake of the left lobe, displaying a “hot” nodule pattern

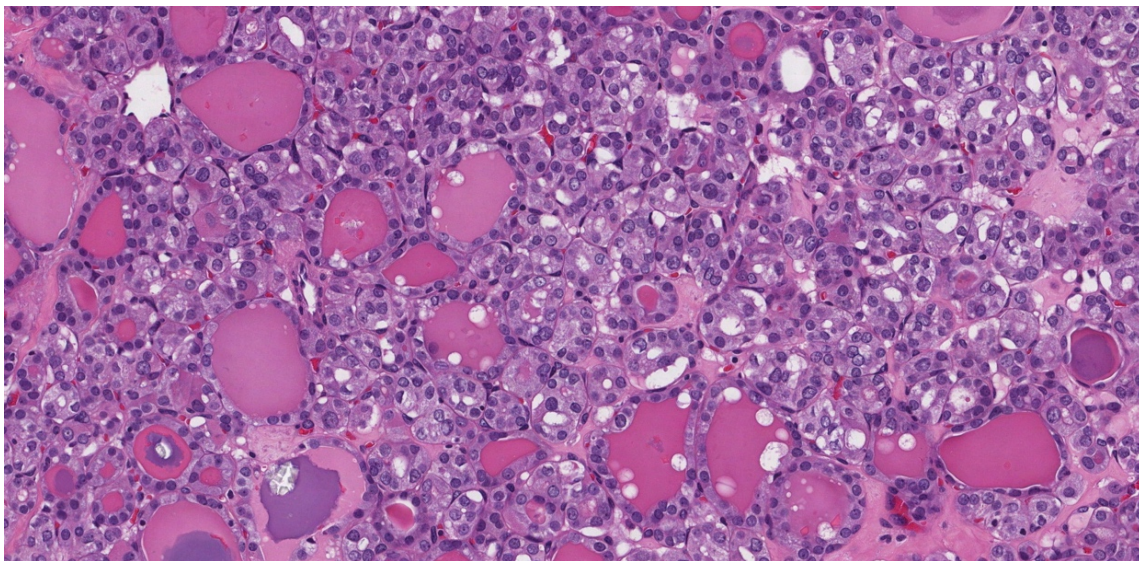


Figure 2: Histological appearance of the surgical specimen showing a folliculo-papillary architecture with typical nuclei, eosinophilic colloid, and vascular emboli.

Discussion

Thyroid nodules are a common condition, predominantly affecting women and older individuals. Their discovery may occasionally be associated with hormonal imbalance, particularly hyperthyroidism related to an autonomously functioning hyperactive nodule. Nearly 90% of these nodules are benign in nature (3). The initial evaluation of such nodules relies on measuring serum TSH and performing a cervical ultrasound; when TSH is suppressed, ^{99m}Tc Pertechnetate or radioactive iodine-123 scintigraphy is indicated to distinguish hyperfunctioning “hot” nodules from cold nodules (4).

Traditionally, hot nodules have been considered almost invariably benign. This assumption stems from scintigraphic studies conducted between the 1960s and 1980s on heterogeneous cohorts of patients with thyroid nodules, which estimated the malignancy risk at less than 1% (5) (6). However, more recent literature reports a higher prevalence of malignancy within these nodules, ranging from 1% to 10.3%, with an average of 3.1% according to Mirfakhraee et al. (7), and up to 8.5% according to Dirikoc et al. (8). A major meta-analysis involving more than 6,600 nodules confirmed that although the malignancy risk in hot nodules is lower (approximately 55% less than in cold nodules), it is not zero (9). Furthermore, a recent case report highlights that the association between papillary thyroid carcinoma and hyperthyroidism remains exceptional, with a prevalence reported in the literature between 0.2% and 8.3% depending on the series (10). These findings challenge the classical notion of a negligible risk and suggest that a small but measurable proportion of cancers may arise in this clinical context.

The mechanisms underlying this association remain controversial. Some molecular hypotheses propose a combined role of activating mutations of the TSH receptor and RAS (G12C) in both tumorigenesis and the hyperfunctionality of the nodules (11). Other studies have identified BRAF V600E mutations in hot nodules harboring papillary carcinoma, suggesting a possible interaction between oncogenic signaling pathways and functional regulation (12).

Moreover, the potential role of iatrogenic factors particularly synthetic antithyroid drugs (ATDs) has been explored in several studies, though no causal relationship has been clearly demonstrated. Large epidemiological studies and systematic reviews have not shown any increased risk of thyroid cancer associated with ATD exposure, regardless of dose or duration (13). Similarly, cohort analyses conducted in hyperthyroid patients treated with antithyroid drugs (ATDs) report an overall increased risk of certain cancers, but no specific effect on thyroid carcinogenesis, suggesting that the hyperthyroid state itself plays a more significant role than the treatment (14). Thus, to date, ATDs are not considered a factor promoting tumor transformation in autonomous nodules; malignancy appears to arise primarily from intrinsic mechanisms within the nodule, related to the acquisition of oncogenic mutations.

In recent years, ultrasound classification systems for thyroid nodules such as EU-TIRADS, ACR-TIRADS, and C-TIRADS have made it possible to estimate malignancy risk based on sonographic features (shape, margins, calcifications, vascularization, etc.) (15). A study involving more than 10,000 nodules demonstrated that TIRADS systems offer reasonable sensitivity and specificity for identifying nodules at risk (16). Available data show that the correlation between functional status and TIRADS score remains limited. A German study conducted by Noto B. et al. in euthyroid patients reported that among nodules considered to require fine-needle aspiration based on TIRADS classifications, between 6% and 8% were actually hyperfunctioning on scintigraphy (17). A complementary study by Schenke S. et al. examined the classification of autonomous thyroid nodules in a context of hyperthyroidism using the TIRADS system. The authors reported that 83.5% of these nodules were classified as TIRADS 4A or higher, corresponding to a moderate to high level of ultrasound suspicion (18).

This observation, which appears paradoxical at first glance, challenges the paradigm that hot nodules are systematically benign, suggesting that their ultrasonographic phenotype may sometimes exhibit features similar to those of malignant lesions (7). In a broader review, Lee et al. reported that among 77 malignant hot nodules, only 36.7% displayed ultrasound criteria clearly suggestive of malignancy, implying that a non-negligible proportion of these lesions would today be classified within low-risk categories (TIRADS 2–3) (19). Similarly, Mirfakhraee et al. described a case of an autonomously functioning hyperactive nodule that appeared isoechoic, well defined, and hypervascular on ultrasound a profile compatible with a low to intermediate risk (equivalent to a low TIRADS score) yet histological examination revealed a follicular thyroid

carcinoma (7). Our case aligns fully with this continuum: it concerns a papillary thyroid carcinoma arising within an autonomously functioning hyperactive nodule whose ultrasound features appeared only moderately suspicious (EU-TIRADS 3), and which had initially been interpreted as benign. These findings reinforce the idea that even when a hot nodule is classified as TIRADS 3, the possibility of malignancy cannot be completely dismissed (estimated risk around 2–4% according to European Thyroid Association (ETA) guidelines), particularly in the presence of compressive symptoms, increasing size, or specific clinical context (20). This case therefore illustrates the limitations of approaches relying exclusively on hyperfunctionality or a low TIRADS score to rule out the risk of thyroid cancer.

In parallel, the correlation between functional status and Bethesda cytological classification remains difficult to establish. Current guidelines do not recommend routine fine-needle aspiration (FNA) of hyperfunctioning nodules, which explains their underrepresentation in large Bethesda cohorts. However, the ATA and ETA emphasize that the presence of suspicious ultrasound features (microcalcifications, hypoechogenicity, irregular margins, lymphadenopathy, elastography findings) justifies targeted cytological evaluation even if the nodule is hot, followed by standard management protocols for differentiated papillary carcinoma in the event of histological confirmation (21) (22).

This difficulty in correlation echoes the conclusions of Yousefi et al., who highlight that neither ultrasound (TIRADS) nor cytology (Bethesda) alone is sufficient to predict malignancy, particularly in areas of diagnostic uncertainty (23). Their integrative model combining clinical data with ultrasound and cytological features significantly improves discrimination between benign and malignant lesions (Area Under the Curve “AUC” 0.9, indicating excellent diagnostic performance) and markedly reduces the proportion of indeterminate nodules, especially within Bethesda III–IV categories (24). In our case, the hot nodule did not exhibit ultrasound features suggestive of malignancy. The surgical indication was based on its plunging nature, which caused compressive symptoms. The discovery of the papillary carcinoma was therefore incidental, revealed only on postoperative histological examination. Surgical series support this observation. According to Liu J. et al., the proportion of cancers diagnosed after excision of hot nodules ranges between 10% and 34%; most correspond to small papillary or follicular carcinomas, incidentally discovered on pathological examination performed after surgery for hyperthyroidism (25). The ETA guidelines also emphasize individualized monitoring of hot nodules that are neither surgically treated nor managed with radioiodine therapy. Follow-up should focus on growth (an increase $\geq 20\%$ in at least two dimensions or $>50\%$ in volume), ultrasound changes, the appearance of lateral lymphadenopathy, or compressive symptoms. The use of ultrasound classification systems, such as EU-TIRADS, is recommended to guide decisions regarding biopsy (19) (26). Radioiodine therapy plays a key role in the management of differentiated hyperfunctioning thyroid carcinomas. Recent recommendations advise reserving this treatment for tumors with intermediate or high

risk, considering tumor size, vascular invasion, and unfavorable histoprognostic features (27). In our case, the presence of a classic papillary carcinoma classified as pT2 with vascular emboli places the patient in an intermediate-risk category, for which a 3.7 GBq radioiodine treatment is consistent with international guidelines. The objective is both to ablate residual thyroid tissue, treat potential micrometastases, and facilitate subsequent follow-up through thyroglobulin monitoring and imaging (22). Paradoxically, the favorable iodine uptake profile of hyperfunctioning nodules constitutes an advantage for the effectiveness of radioiodine therapy in this context. Available data further suggest that the survival prognosis of hyperfunctioning carcinomas depends primarily on tumor stage and histological type, rather than on the hyperfunctioning nature itself. In the historic series by Als et al., involving 19 toxic carcinomas, the 5-year overall survival was lower than in a larger cohort of euthyroid differentiated carcinomas (56% vs. 94.5%); however, this difference markedly diminished after adjustment for age, sex, and histology (5-year survival \approx 74%) (28). Other series and reviews show that when the tumor is diagnosed at a localized stage and treated with complete surgery followed, when appropriate, by radioiodine therapy, the prognosis approximates that of papillary or follicular carcinomas of the same stage (29) (30). In the systematic review by Liu et al., including 43 primary hyperfunctioning carcinomas and 28 metastatic forms, most patients were treated with total thyroidectomy followed by I-131 radioiodine therapy, and only 14 out of 43 experienced recurrence during a median follow-up of approximately 44 months, suggesting satisfactory clinical and tumor control after surgery plus radioiodine treatment (31). In general, the 10-year disease-specific survival of differentiated thyroid carcinomas remains around 80–95% depending on the series (32), placing cases revealed within a toxic nodule in an overall favorable prognostic category, provided that complete treatment is performed (surgery + RAI when indicated + moderate TSH suppression). In this context, the therapeutic pathway of our patient total thyroidectomy followed by a 3.7 GBq ^{131}I treatment, then suppressive L-thyroxine therapy with sustained thyroglobulin negativity is consistent with these data. It demonstrates that a malignant autonomously functioning hyperactive nodule benefits from the same management principles as a “classic” papillary carcinoma, with excellent prognosis when the disease is diagnosed at a localized stage and when the combined strategy of surgery + radioiodine therapy is carried out in accordance with current recommendations (33).

Conclusion

The association between a toxic thyroid nodule and papillary carcinoma is rare but now well documented. The long-held dogma that a hot nodule is always benign must be reconsidered in light of recent meta-analyses. Although the risk of malignancy is low, it is real and warrants heightened clinical and ultrasonographic vigilance. An integrated approach combining clinical context, ultrasound, scintigraphy, and targeted cytology remains the most rational strategy.

Future management of thyroid nodules in general and of so-called “autonomous” nodules in particular should benefit from advances in molecular genomics. These developments offer promising perspectives for a better understanding of carcinogenesis mechanisms and for the development of complementary diagnostic tools, such as molecular tests, despite their current limitations.

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