

Case Report

Papillary thyroid carcinoma presented as a hypercaptant nodule: a case report

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ABSTRACT

Hot thyroid nodules are mostly benign and rarely show a malignant nature. Here we present the case of a 45-year-old man with a hypercaptant but ultrasound suspicious nodule; he underwent fine needle aspiration (FNA) and subsequent thyroidectomy. Pathology revealed a papillary thyroid carcinoma (PTC) with focal tall cell features, positivity to BRAF V600E and focal hyperspression of p53. A multidisciplinary clinicopathological approach is crucial for the correct diagnosis.

1. Introduction

Thyroid nodules are frequently encountered in the general population worldwide; most are benign lesions, while a small percentage (5%–15%) are malignant (Alexander et al., 2004). Thyroid scintigraphy is an imaging method used to define the nature of thyroid nodules by assessing the ability of the cells to capture or not to capture iodine or its analogues (Technetium-99) (Intenzo et al., 2012); hypercaptant nodules on scintigraphy, also referred to as ‘hot’ nodules, present a benign behaviour and have been associated with a low risk of malignancy (Chang et al., 2018).

2. Case report

A 45-year-old-man suffering from toxic goiter under therapy with methimazole (Table 1) went to the endocrinology unit for the appearance of a voluminous neck nodule for which he underwent an initial ultrasound examination that showed a 35-mm nodule consisting of two confluent nodules, with an inhomogeneous, hypoechoic structure, with a punctiform hyperechoic foci with irregular and sometimes blurred borders (Fig. 1). The study with Technetium-99 scintigraphy showed an inhomogeneous area of hyperfixation occupying 2/3 of the left lobe of the thyroid, as well as a small area of the upper third of the same lobe (Fig. 2). In contrast, the contralateral lobe showed increased fixation of

the radiopharmaceutical in the lower half, with a reduction in the remaining parenchyma.

The workout subsequently included a fine needle aspiration (FNA) examination. Cytology showed papillary-like structures and sheets of thyrocytes with voluminous, moderately pleomorphic nuclei with finely distributed chromatin, frequent grooves and rare pseudo-inclusion (Fig. 3). Immunohistochemical investigations performed on cell block samples showed positivity for the markers HBME1 and Galectin3. Due to morphological and immunohistochemical findings strongly compatible with papillary thyroid carcinoma (Category VI of Bethesda System), the patient underwent total thyroidectomy.

3. Gross pathology

On macroscopic observation, the thyroid gland showed a left lobe increased in size compared to the right (5.5 × 3 × 3 cm vs 4.5 × 2.5 × 2.7 cm), and at the cut surface, it was possible to observe two confluent nodules with a total maximum size of 2.6 × 3 × 1.8 cm (Fig. 4).

4. Histology

The histological examination of the macroscopically described nodule consisted of neoplastic proliferation of elements of thyrocytes nature aggregated in papillae and rare micro follicles (Fig. 5), with

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Table 1
Thyroid function test.

	Value	U.M.	V.N.
F-T3	3.82	pg/ml	2.30–4.20
F-T4	1.56	ng/dl	0.89–1.76
TSH	0.29	μIU/ml	0.55–4.78
PTH	61.50	pg/ml	11.00–67.00
CALCITONIN	<2.00	pg/ml	<8.40

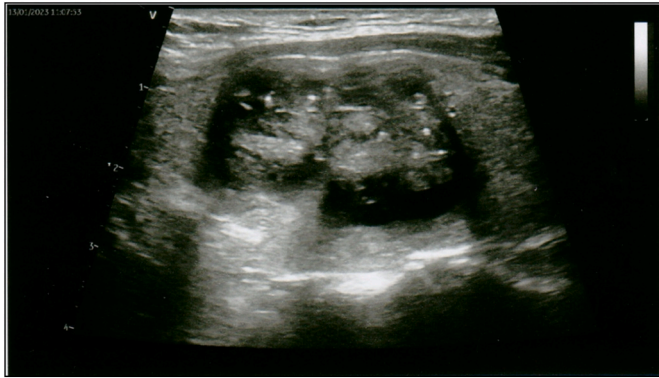


Fig. 1. Ultrasound examination.

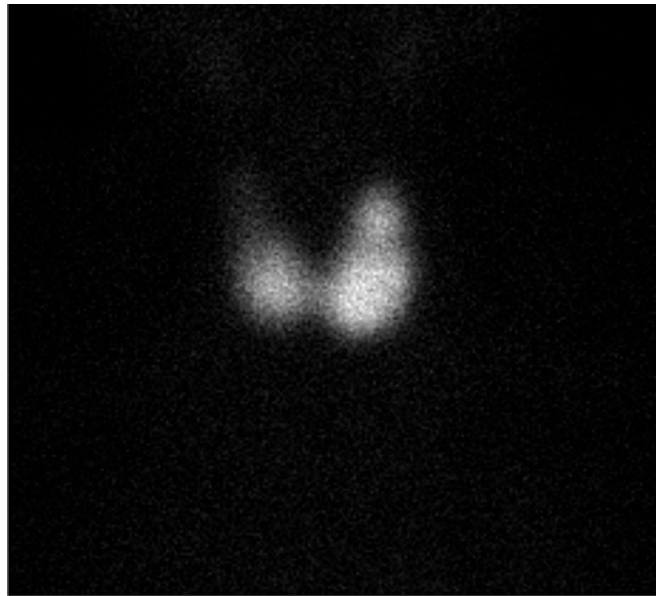


Fig. 2. Technetium-99 scintigraphy.

nuclear features typical of papillary carcinoma, within which there was an area of large eosinophilic cytoplasm and cylindrical shape (tall cells) (Fig. 5b). The neoplasm lacking a capsule showed extensive central regressive phenomena (hemorrhage, sclerosis and microcalcifications) with an infiltrative pattern but without extending beyond the gland border and without foci of angioinvasion. The remaining thyroid parenchyma showed mild architectural disorder with focal indirect signs of colloid resorption and scattered foci of chronic lymphocytic inflammation, sometimes organized in follicular aggregates with activated germinal centers. A minute neoplastic spot of about 1 mm was also present at the isthmus level. Two peri-isthmus lymph nodes showed regular morphology.

Immunohistochemical investigations revealed positivity for the BRAF V600E marker and focal overexpression of p53 (Fig. 6). The final

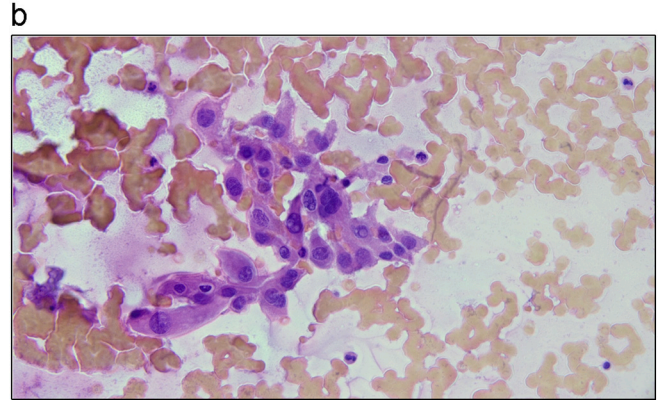
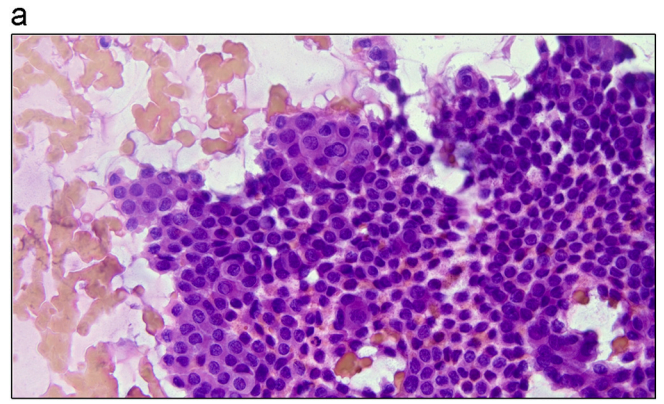


Fig. 3. a: Cytology; E&E.
b: Cytology; E&E.

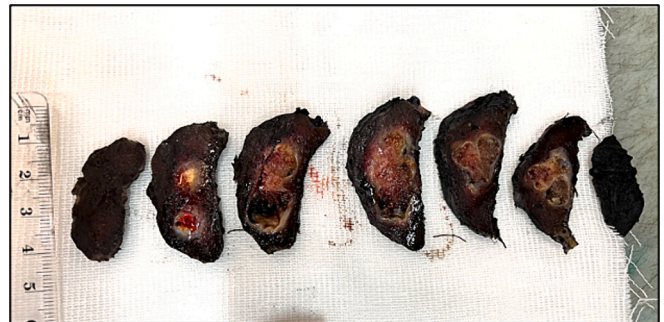


Fig. 4. Surgical specimen.

diagnosis was multicentric infiltrating papillary carcinoma of classical type with high cell aspects in probable Graves' disease.

5. Discussion

Thyroid nodules are common clinical conditions, and 90 % are generally benign, occurring more in women and the elderly population (Burman and Wartofsky, 2015; Walsh, 2016).

Thyroid scintigraphy is an imaging method that uses radioactive iodine or Technetium-99 in cases of a palpable nodule or if the cause of hyperthyroidism is unknown (Lee and Pearce, 2023). The pattern of radiopharmaceutical uptake can distinguish nodules into hyperfunctioning (hot) or hypofunctioning (cold) (Gharib and Papini, 2007). Hot thyroid nodules account for approximately 5–10 % of thyroid nodules and, in contrast to hypofunctioning nodules, they generally present a benign nature (Popoveniuc and Jonklaas, 2012); thus, they seldomly are thought to manifest as malignant lesions (Cooper et al., 2009). In a 2013

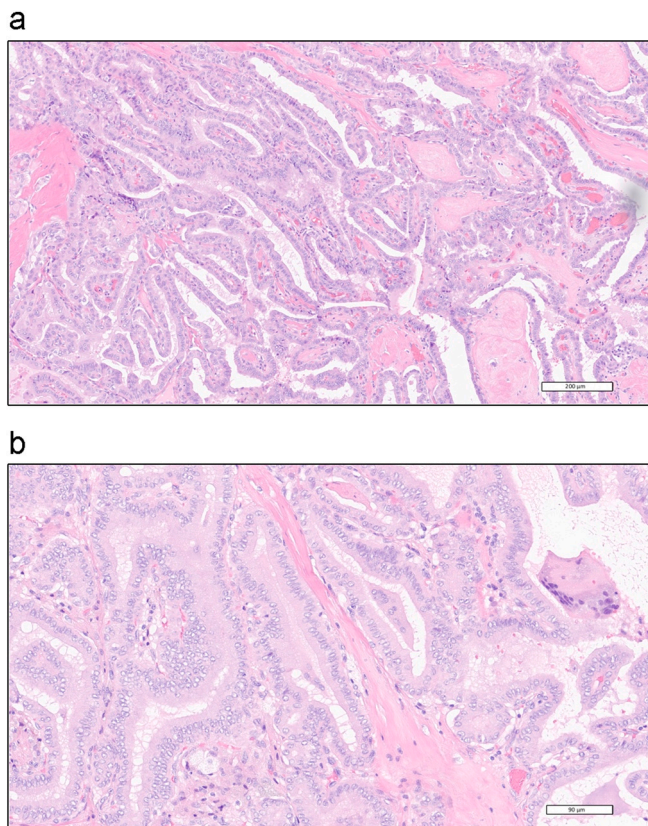


Fig. 5. a: Histology; E&E.
b: Histology, tall cells; E&E.

review by Mirfakhraee et al., the percentage of malignancy within hot nodules ranged from 0 % to 12.5 % with an average of 3.1% (Mirfakhraee et al., 2013); a more recent 2015 paper by Dirikoc et al. states that this percentage is 8.5% (Dirikoc et al., 2015). As concerning the histotype, most of the literature agrees that papillary carcinomas are the ones usually arising in a hypercaptating nodule; the patients are most frequently young and female subjects (Mirfakhraee et al., 2013; Osorio et al., 2021); however, a large percentage of cases of about 40–46 % turn out to be follicular variants, which constitutes about 10 % of all thyroid nodules as indicated by the study of Liu et al. (Liu et al., 2019) Osorio et al. calculated that a clinical diagnosis of toxic nodular goiter, nodular lesions >10 mm and a histotype compatible with follicular carcinoma increase the probability of diagnosing a carcinoma within a hot nodule (Osorio et al., 2021).

Our case is the first in the literature of hypercaptant papillary carcinoma with aberrant and focal overexpression of p53 protein and the second of tall cell variant papillary carcinoma with BRAFV600E mutation (Shinkai et al., 2021).

The association between hyperthyroidism and thyroid carcinoma is rare (Lima et al., 2018). The incidence of malignancy in Graves' disease and toxic multinodular goiters is 2 % and up to 9 %, respectively (Stocker, 2003; Cerci et al., 2007).

Although the causes are still unknown, a study by Niepomniszcze et al. hypothesises that the combination of the TSH receptor mutation and the RAS (G12C) mutation may synchronously play a role in both the process of carcinogenesis and the hyperfunctionality of the malignant nodule (Niepomniszcze et al., 2006). In particular, the TSH receptor mutation activates the intracellular cAMP cascade with hormone production by tumour cells and subsequent hyperthyroidism (Kadia et al., 2016). The belief that a hot nodule only rarely harbours malignancy stems from scintigraphic studies conducted between the 1960s and 1980s on heterogeneous populations of patients with thyroid nodules

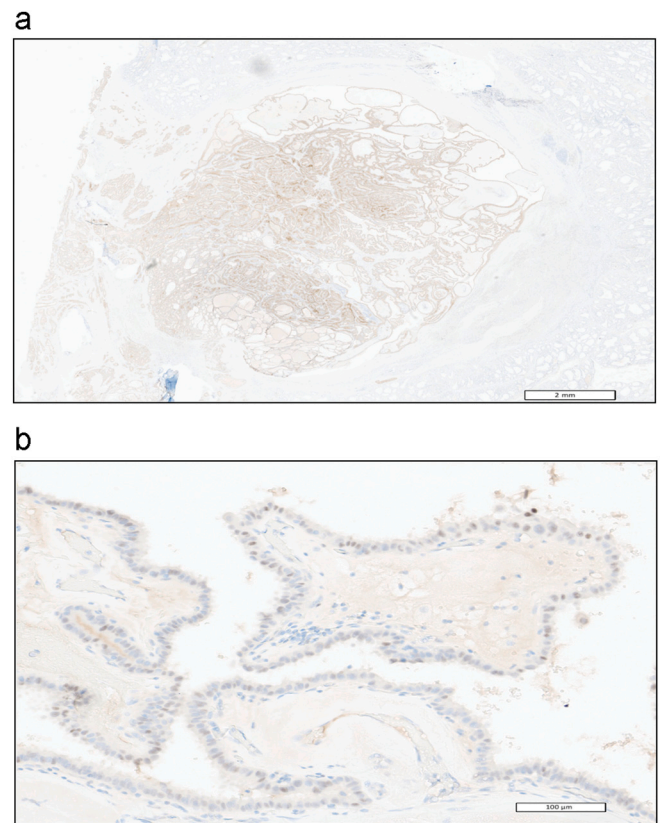


Fig. 6. a: BRAFV600E; IHC.
b: p53; IHC.

(Ashcraft MW VHA, 1981; JN, 1960); however, since these studies, there has been an increase in the use and improvement of ultrasonographic techniques (Lau et al., 2021). To date, the risk of malignancy of a hyperfunctioning nodule may be underestimated precisely because of the belief in a rare correlation between thyroid carcinoma and hot nodule on scintigraphy (Gharib et al., 2010), resulting in the non-recommendation to perform FNA or thyroidectomy on this type of nodule (Dy et al., 2018). Moreover, most of those studies are case reports, so the results should be interpreted with care (Liu et al., 2019).

CRediT authorship contribution statement

Maria Letizia Lai: Data curation. **Jacopo Caschili:** Writing – original draft. **Priscilla Baldussu:** Writing – original draft. **Alessandra Serra:** Data curation. **Lucia Secci:** Data curation. **Pietro Giorgio Calò:** Data curation. **Clara Gerosa:** Supervision. **Daniela Fanni:** Writing – review & editing, Supervision.

Declaration of competing interest

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Data availability

The authors are unable or have chosen not to specify which data has been used.

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