Newly described thyroid tumours and variants

Catarina Eloy

Abstract

It is rare to have the opportunity to observe a new clinic-pathological entity in the thyroid since the second half of the twentieth century. This review will be focused on the description of new entities and new morphological variants of thyroid tumours, first published in the twenty-first century, that were not included in the 2004 WHO Classification of tumours of endocrine organs.

Keywords hobnail variant of papillary carcinoma; neuroendocrine tumour; review; small cell tumour; thyroid

Introduction

The "good old days" in which many new thyroid tumours and their variants were described took place in the second half of the twentieth century. Since then, it is exceptionally rare to have the opportunity to observe a new clinico-pathological entity. The fading of this "morphologic" period, gave rise to the beginning of the identification of tumour molecular alterations. With the exception of somatic mutations of *BRAF* in papillary thyroid carcinoma (PTC), germline and/or somatic mutations of *RET* in medullary carcinoma and germline and/or somatic mutation of *APC* in cribriform-morular variant of PTC, the identified molecular alterations turned out to be not diagnostic markers of a tumour type or variant but are improving our understanding of neoplastic transformation and progression of thyroid tumours. Recently, much attention has been focused on molecular profiles associated with response to therapy.

At this point, more than 20 years after the seminal findings on the molecular profiles of PTC (*RET/PTC* rearrangement) and anaplastic carcinoma (*p53* mutation), it is no longer relevant to describe a new entity or a morphologically distinct variant if it does not have a particular molecular signature or if it is not characterized by a distinct prognosis or by a specific response to therapy. The exceptions are the thyroid tumour variants that, by similarity with morphological patterns of tumours of other organs, may be confused with metastatic disease to the thyroid. In any case, we are always considering exceptionally rare tumours.

This review will focus on the description of new entities or morphological variants of thyroid tumours, first published in the twenty-first century that were not included in the 2004 WHO Classification of tumours of endocrine organs.

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Morphological variants of follicular tumours

Described for the first time in 2005, the **meningioma-like tumour of the thyroid**[1] was considered a morphological variant of follicular adenoma. The meningioma-like tumour of the thyroid is an encapsulated tumour that can be potentially confused with the transitional meningioma (primary of the neck region or metastatic) as the name implies, or with other also rare spindle cell tumours such as the spindle cell variant of medullary carcinoma, the spindle cell tumour with thymus-like elements (SETTLE) or the solitary fibrous tumour. The peculiar arrangement of bland looking ovoid cells in a whorled pattern around thick walled blood vessels (Figure 1) may also give this tumour a similar appearance to vascular tumours of the pericytic group. The apparently benign behaviour of the two reported cases, the focal immunohistochemical staining of the tumour cells for TTF-1 and thyroglobulin, and the coexistence of the spindle cells with well differentiated follicles, favours the interpretation that the meningioma-like tumour of the thyroid is a morphological variation of the spindle cell metaplasia occurring occasionally in follicular adenomas.

The almost vanished follicular carcinoma also has a new widely invasive variant with a particularly aggressive behaviour that was described as having an unusual glomeruloid pattern of growth.[2] The **glomeruloid variant of follicular carcinoma** is an infiltrative and angioinvasive neoplasm characterized by follicles with round to oval epithelial tufts growing within, often supported by fibrovascular cores, mimicking the renal glomerulus, admixed with elongated colloid-empty follicles (Figure 2). These features had been illustrated but not commented in one of the figures of the insular variant of follicular carcinoma in the 1988 WHO – Histological Typing of Thyroid Tumours. The tumour cells disclose a pseudostratified organization and expressed TTF-1, apical thyroglobulin and focal WT-1 nuclear staining.[2] The case published by Cameselle-Teijeiro et al. in 2008 also harboured a *PAX8/PPARgamma* rearrangement.[2] The resemblances of this thyroid tumour with kidney tumours, here highlighted by the *PAX8* alteration and WT-1 expression, are epitomized by the primary thyroid-like follicular carcinoma of the kidney.

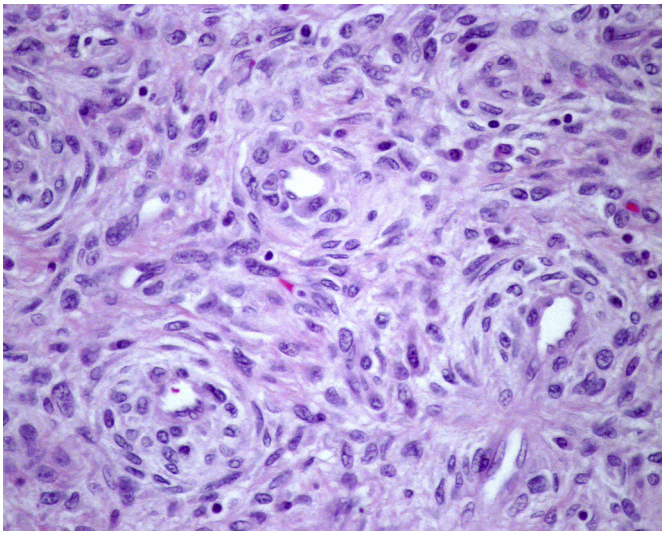

Figure 1 The whorled pattern of meningioma-like tumour of the thyroid (H&E, 400×).

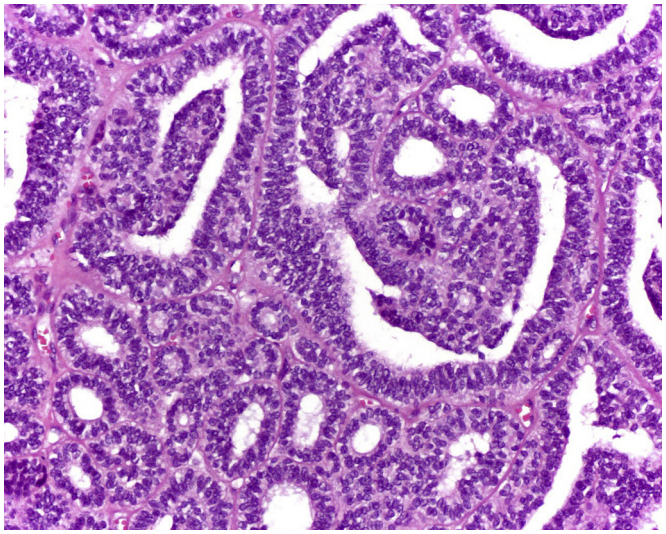

Figure 2 Glomeruloid structures in the glomeruloid variant of follicular carcinoma (H&E, 200×).

Morphological variants of papillary carcinoma

PTC remains the thyroid tumour with the largest amount of variants or distinct tumour growth patterns, not all with relevant prognostic meaning but which may be important for recognition of the tumour type. An example of such apparently non-clinically relevant variants is the **angiomatoid PTC** that develops in the context of Hashimoto's thyroiditis.[3] The angiomatoid PTC can be confused with a vascular tumour if the characteristic nuclear features of PTC in the cells lining the vascular-like spaces are not searched at high magnification (Figure 3). The vascular-like spaces can display a prominent anastomosing pattern, are lined by TTF-1 and thyroglobulin positive, cuboidal to flat cells, and are surrounded by a prominent collagenous stroma.

The group of the primary thyroid tumours of the salivary gland-type, that includes the Warthin-type oncocytic PTC and the mucoepidermoid thyroid carcinoma, has recently been enriched by the **adenoid cystic pattern in PTC**.[4] This unique growth pattern of PTC that mimics adenoid cystic carcinoma of salivary glands, particularly on fine needle aspiration biopsy, is characterized by the presence of basement membrane-like, thyroglobulin-negative material within the lumina of follicular structures and surrounding solid, cribriform and trabecular nests of the tumour cells with PTC nuclear features. The adenoid cystic carcinoma-like growth pattern may co-exist with other patterns of PTC such as the columnar cell and the cribriform-morular pattern.

In contrast to the above mentioned apparently non-clinically relevant new variants, the **hobnail/micropapillary variant of PTC** reported by Motosugi et al. in 2009 is a rare, aggressive and locally invasive form of PTC in which >30% of the tumour cells have hobnail features.[5–7] These tumours are often multifocal and are constituted by complex papillary structures lined by cells with eosinophilic cytoplasm and apically placed nuclei that produce a surface bulging, resulting in the so-called hobnail appearance (Figure 4). The micropapillary pattern often co-exists with this hobnail appearance and consists of papillary tufts, with or without fibrovascular cores, lined by cells with loss of polarity and PTC-type nuclei (Figure 5). In cytological specimens, the cells are arranged in discohesive papillary-like clusters or in micropapillary groups, exhibiting "tear-drop" or "comet-like" cytoplasm and displaying nuclei with pseudoinclusions and grooves. Some authors highlighted the resemblance between the hobnail/micropapillary pattern and other variants of PTC, such as the tall cell variant[8] and the oncocytic variant, as the neoplastic cells also have eosinophilic cytoplasm and are packed with mitochondria.[9] In the series studied by Asioli et al.,[6] the hobnail pattern co-existed with tall/columnar cell pattern or with diffuse sclerosing pattern. The same authors reported that all cases of hobnail/micropapillary PTCs expressed thyroglobulin, TTF-1, HBME-1 and p53; *BRAF* mutation was present in four out of seven cases.[6] In the series of Lee et al. the *BRAF* V600E mutation was found in eight cases (80%) of hobnail/micropapillary PTC whereas no ALK fusion or TERT promoter mutations were detected.[7] The literature review of cases of hobnail/micropapillary PTC performed by Lee et al. documented disease-specific survival rates of 83%, 71%, and 54% at 5, 10, and 20 years after the initial surgery, respectively, highlighting the aggressive nature of this new variant.[7]

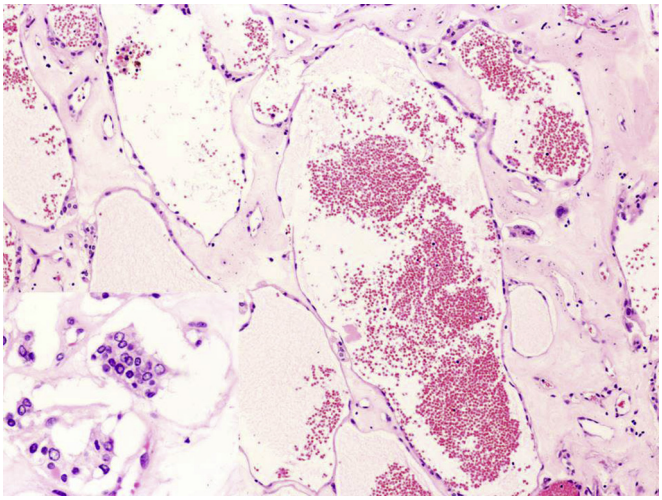

Figure 3 The vascular-like pattern of the angiomatous variant of papillary carcinoma with nuclear pseudoinclusions (H&E, 100×; inset-H&E, 600×).

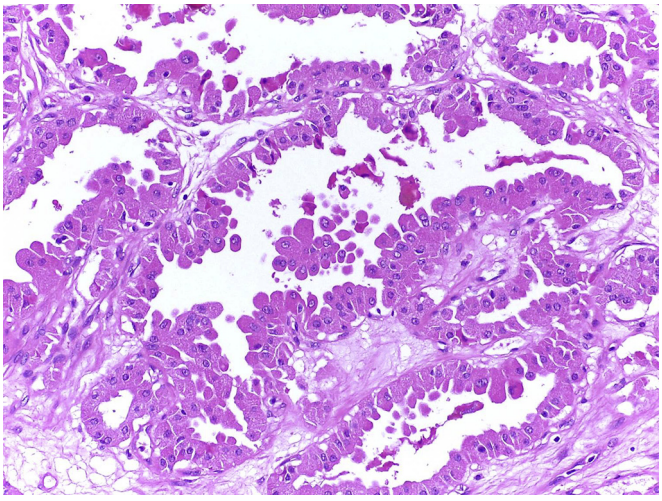

Figure 4 Hobnail features in the hobnail/micropapillary pattern of papillary thyroid carcinoma (H&E, 400×).