Pitfalls in the surgical pathologic diagnosis of papillary thyroid carcinoma

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Abstract

While the surgical pathology examination of the thyroid gland for papillary carcinoma may seem, on its surface, to be relatively straightforward, in reality it is fraught with diagnostic traps. Avoidance of these pitfalls is necessary for guiding the surgeon and endocrinologist to the appropriate treatment and follow up. This review will detail a selected group of some of the more commonly encountered challenges in making the diagnosis of papillary thyroid carcinoma from a busy head and neck pathology consultation practice.

Keywords papillary thyroid carcinoma; pitfalls.; thyroid gland

Introduction

On its surface, the surgical pathology of the thyroid gland may appear to be relatively straightforward, perhaps even mundane. After all, the vast majority of cases that pass through a surgical pathologist's microscope are either obviously benign (most commonly multinodular hyperplasia) or obviously malignant (most often conventional papillary carcinoma). Moreover, unlike cytopathologists who contend with a limited sampling of detached cells with innumerable potential artifacts (**see accompanying review in this issue by VandenBussche and Ali**), surgical pathologists have the benefit of architectural features and the entire lobe or gland to review. Despite these facts, however, any diagnostician who regularly encounters thyroid gland specimens knows that this area of pathology is rife with its own unique set of challenges. Indeed, even seemingly banal cases of multinodular hyperplasia or conventional papillary carcinoma not infrequently have features that may trap the pathologist into erroneous diagnoses. Compounding the problem, some of these pitfalls, while well known to thyroid pathology consultants, are not well described in the thyroid pathology literature. This review will focus on a selected group of the most common and/or most treacherous pitfalls in the reaching the diagnosis of the most common thyroid malignancy: papillary thyroid carcinoma (PTC). These will be divided into two main groups – pitfalls in interpretation of cyto-architectural features and pitfalls in interpreting invasive growth – with an emphasis on strategies for resolving these diagnostic dilemmas.

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Conflicts of interest: none.

Cyto-architectural pitfalls in diagnosing PTC

Papillary thyroid carcinoma (PTC) is, by far, the most common malignant neoplasm of the thyroid gland, and the classic (i.e., conventional) form is the most common subtype.[1] Its diagnosis is based on both architectural as well as cytologic findings, and while usually straightforward, for each feature there is a corresponding diagnostic pitfall (Table 1).

Benign papillary hyperplasia

The presence of papillary architecture is the most important feature of conventional PTC; indeed, it is the feature from which the neoplasm derives its name. A papilla, of course, is defined as a finger-like growth lined by epithelium and containing a fibrovascular core. The mere presence of papillary architecture, however, is not entirely diagnostic for PTC. Papillary hyperplasia is finding seen in a number of benign conditions, most commonly in Graves disease (diffuse hyperplasia) but also in adenomatoid nodules and follicular adenomas (especially those with oncocytic or Hurthle cell alterations).

Benign papillary hyperplasia is distinguished from PTC in several ways. First, recognition of the distribution of the papillary growth is helpful. Its presence diffusely throughout the gland supports a benign process; if one was to regard the papillary hyperplasia of Graves disease as PTC, for example, the entire gland would have to be called malignant. In contrast, papillary growth in an infiltrative tumour inducing a fibrotic stromal reaction is much more in keeping with PTC. Second, the characteristics of the papillae themselves are helpful. Specifically, in benign papillary hyperplasia the papillae are short, stubby, and simple, contrasting with the long and complex (with secondary and tertiary branching) papillae of PTC (Figure 1a–b). In addition, the papillary structures of benign papillary hyperplasia tend to point inward towards the center of a dilated follicular structure (so-called centripetal growth), in contrast with the more haphazard arrangements of papillae in PTC (Figure 1a–b).[1,2] Finally, the nuclei in benign papillary hyperplasia are small, round, dark, and basally oriented, unlike what is seen in PTC where tumour nuclei are not well oriented in the papillary fronds, and where they exhibit the characteristic nuclear features of PTC (described in detail below) (Figure 1a–b).[2] It is worth noting that immunohistochemistry (e.g., CK19, galectin-3, HBME-1) is of limited value in the differential diagnosis between PTC and benign papillary hyperplasia.[3]

Intrafollicular lamellated concretions (pseudopsammoma bodies)

The psammoma body is another important diagnostic feature of conventional PTC. This lamellated calcification is felt to represent the calcified tip (a "tombstone") of a necrotic papilla of PTC. The psammoma body is such a specific finding of PTC that its presence in the thyroid interstitium or within a cervical lymph node is believed to be very compelling evidence for the existence of PTC within the ipsilateral thyroid lobe.

Uncommonly, microscopic structures virtually identical to psammoma bodies are seen in benign thyroid processes, and they are known as intrafollicular lamellated concretions or pseudopsammoma bodies. These peculiar structures appear to represent foci of inspissated colloid that have undergone

Cyto-architectural features of PTC and corresponding diagnostic pitfalls

Feature of PTC	Pitfall
Papillary architecture	Benign papillary hyperplasia
Psammoma bodies	Intrafollicular lamellated concretions (i.e., pseudo-psammoma bodies)
Nuclear atypia (e.g., chromatin clearing, enlargement, grooves)	• Reactive changes (e.g., setting of Hashimoto thyroiditis, Graves disease) • Hurthle cell alterations • Frozen section artifact • Hyalinizing trabecular adenoma
Intranuclear pseudoinclusions	Nuclear vacuoles (i.e., bubbles)

Table 1

calcification, and they are of no known clinical significance. If one is aware of their existence, intrafollicular lamellated concretions are easily distinguished from psammoma bodies. Unlike true psammoma bodies, intrafollicular lamellated concretions are not located at the tips of papilla or within the thyroid interstitium, but rather within the follicles themselves (Figure 1c–d).[2] For unclear reasons intrafollicular lamellated concretions are particularly common in benign oncocytic (Hurthle cell) proliferations, so recognizing this setting is helpful. Finally, intrafollicular lamellated concretions can typically be seen in varying stages of evolution, with foci of inspissated colloid without calcification, foci showing early calcification, as well as more fully developed pseudo-psammomatous calcifications (Figure 1c).[2,4]

Reactive nuclear atypia

PTC is also characterized by a particular form of nuclear atypia, a defining, obligate feature that takes precedence even over the architectural features described above. Specifically, the nuclei of PTC exhibit some combination of these alterations: chromatin pallor, enlargement and elongation, crowding, overlapping, and dyspolarization, and nuclear contour irregularities that may take the form of jagged edges or notches in the nuclear membrane, longitudinal grooves, or protrusions of the cytoplasm into the nucleus (intranuclear pseudoinclusions).

Not all of the listed nuclear features of PTC are present in every case, and importantly, none of the features are, by themselves, entirely specific for malignancy. In fact, it is not uncommon to encounter some degree of nuclear atypia in benign thyroid glands as a reactive change. While reactive atypia is usually fairly mild, at times it can be well developed and reach the level of severity that may be encountered in PTC. Reactive nuclear atypia is most pronounced in Hashimoto thyroiditis (Figure 2a–b). Distinguishing reactive atypia from PTC in this setting depends on recognizing its context: once again, diffuse involvement of the gland argues against PTC. Moreover, the atypia is most severe in the most intense areas of inflammation. While it is true that PTC commonly arises in the setting of

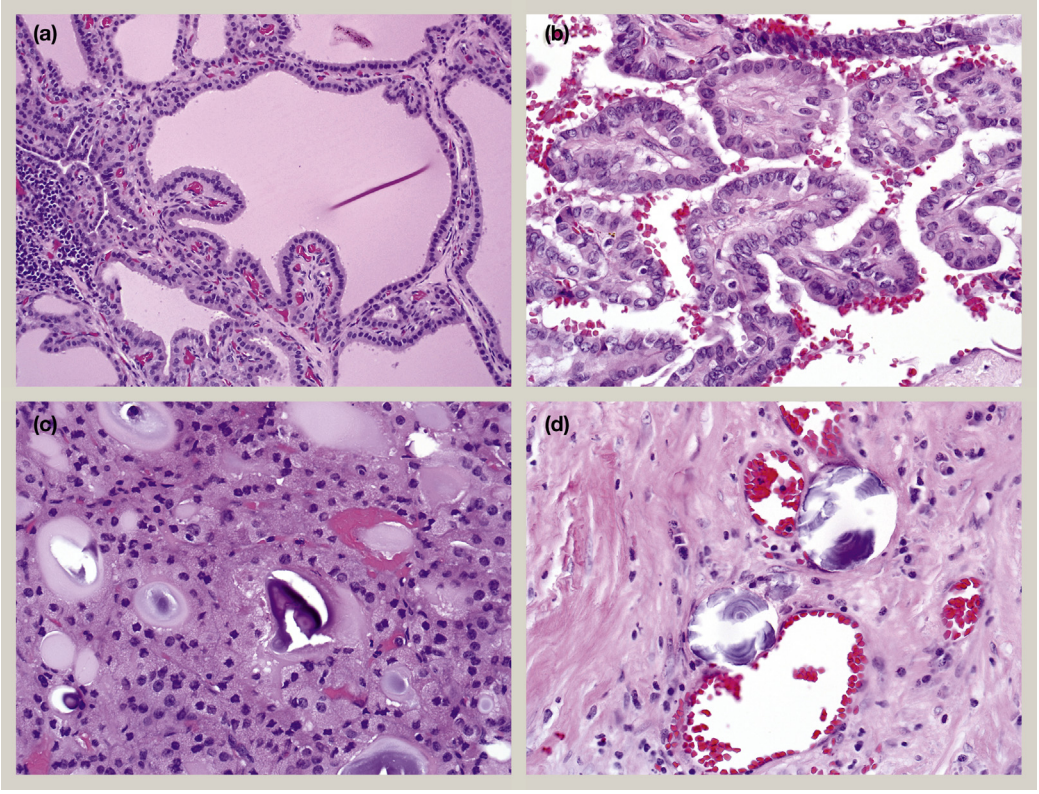

Figure 1 Benign papillary hyperplasia in the setting of Graves disease features short, simple papilla pointing to the center of a dilated follicle and lined by bland nuclei (**a**), in contrast to the complex, haphazard, longer papilla lined by atypical nuclei in papillary carcinoma (**b**). Pseudo-psammoma bodies seen within the follicles of a Hurthle cell proliferation, and in varying stages of development (**c**), unlike true psammoma bodies of papillary carcinoma seen in the interstitium associated with small blood vessels (**d**).