Thyroid intrafollicular neoplasia: A spectrum of morphological appearances from benign cytologic precursors to microscopic papillary carcinoma

Usually, papillary thyroid microscopic carcinoma (PTMC) is diagnosed after surgical intervention of an otherwise benign clinical lesion. The high frequency of PTMC in autotopic series (from 5-35%) and the low incidence of clinically manifest PTMC (< 0.1% lifetime risk) suggest that most thyroid papillary carcinomas never become clinically evident because of their very slow progression.[1] Several important aspects of the biology and behavior of the PTMC have been discussed to better define the terminology.[2] High-resolution ultrasound image combined with FNAC are routinely used to assess subjects at risk (as for people with multinodular goiter, chronic thyroiditis, thyroid adenoma, laterocervical lymph node metastasis, Graves’ disease, hyperparathyroidism or with positive family history of thyroid cancer or exposed to radiation) and allow the early detection of thyroid carcinomas less than 0.5-1 cm in diameter.[3] Nevertheless, most PTMC represent a therapeutic dilemma for clinicians because these lesions are recognized by the pathologist only in the final report after surgical hemithyroidectomy of nodular benign disease. For this reason, to avoid the need for reoperation, total or near-total thyroidectomy is nowadays the procedure of choice during initial surgery for all nodular thyroid disease, even with a presumably negative cytology at the ECO-FNA.[4]

The histological aspect of the earliest recognizable cellular atypia consists of a small single follicle with irregular shape and characteristic dysmetric nuclei with fine chromatin pattern, chromatin clearing, grooves of nuclear membrane and intranuclear inclusions [Figure 1]. Atypical follicles are isolated or aggregate in small clusters, localized in an apparent normal thyroid parenchyma, frequently associated to lymphoid nodular reactive infiltrates. Stromal sclerosing appear as a secondary phenomenon in which it’s possible to see a tubular pattern of the atrophic follicles, cellular polistratification and budding of papillae with a fine fibrovascular stroma and microcalcifications. The follicle pattern and the nuclear abnormality can be identified as mild, moderate or high follicular dysplasia and could represent a better marker for histological and cytological diagnosis.

All these morphological aspects can be defined as “Thyroid intrafollicular neoplasia” (TIN) like has been usually described as CIN in the uterine cervix or PIN in the prostate. The progression of atypical features of follicular epithelial cover a wide spectrum that start with the dispersion of nuclear chromatin and end with the papillary fibro-epithelial pattern. Low-grade and high-grade TIN could represent a morphological test to detect precursors of the incipient thyroid papillary carcinoma still in an early intrafollicular or microscopic stage.[4] However, morphological identification of follicular atypia as precursor of malignancy (TIN) represents a crucial diagnostic cyto-histological problem for pathologists and could help to clarify the biological and clinical significance of the histological report when so-called “incidental” PTMC are detected in a nodular goiter, follicular adenoma, chronic thyroiditis, etc.[4]

These observations are also supported by molecular report that described a strictly relationship between RET/PTC oncogene and the altered nuclear envelope (grooves) and chromatin structure (clearing).[6] Moreover, it has been recently observed that the RET/PTC1 oncogene activates a proinflammatory program with a direct link between a transforming human oncogene, inflammation and malignant behavior.[7,8] Finally, another crucial morphological point that must be stressed in the surgical pathology of the thyroid is the differential
histological diagnosis of nonneoplastic and/or pseudotumoral conditions from malignancy.\(^9\)

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**References**