

Thyroid intrafollicular neoplasia (TIN) as a precursor of papillary microcarcinoma



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BACKGROUND: *The aim of this study was to identify a spectrum of morphological changes from benign reactive follicles to suspected thyroid intrafollicular neoplasia (TIN) and papillary microcarcinoma observed in different pathological processes of the thyroid gland.*

CASE SERIES: *In a retrospective study on a total of 105 cases, occult or incidental thyroid papillary microcarcinoma was found in association with multinodular goiter (52%), chronic thyroiditis (19%), follicular adenoma (19%), parathyroid neoplasia (5%), and no evident thyroid pathology (5%).*

RESULTS: *Atypical follicles are described in various pathological conditions correlating with lymphoid inflammatory infiltration, stromal sclerosis, and hyperplastic or neoplastic follicular nodules. The histological pattern of papillary carcinoma is compared with morphological changes ranging from atrophic and/or reactive thyroid follicles, potential intrafollicular thyroid neoplasia (TIN) and papillary microcarcinoma.*

CONCLUSIONS: *The atypical features of follicular epithelial areas make up a wide spectrum that starts with the dispersion of nuclear chromatin. Low- and high-grade TIN may represent a cytological marker of dysplastic lesions and precursors of thyroid papillary carcinoma when it is still in an early intrafollicular or pre-invasive stage in various pathological processes of the thyroid.*

KEY WORDS: Dysplastic and precursor lesions, Papillary thyroid microcarcinoma, Thyroid intrafollicular neoplasia (TIN), Thyroid neoplasms.

Introduction

The multifocality or intraglandular lymphatic metastases of thyroid papillary carcinoma is well known from the literature¹, but there is evidence from observations of our own and others^{2,3} of a frequent association of papillary carcinoma with various pathological processes of the thyroid gland. Moreover, RET/PTC oncogene expression is seen in adenoma^{4,5} multinodular goiter⁶ and Hashimoto's thyroiditis⁷. The high frequency (from 5% to 35%) of papillary microcarcinoma in autopsic series⁸⁻¹⁰ and the low incidence (<0.1% lifetime risk) of clinically manifest papillary carcinoma¹¹ suggest that most thyroid carcinomas never become clinically evident

because of their very slow progression. High-resolution ultrasonography and FNAC have increased the preoperative diagnosis of occult thyroid carcinoma, however¹².

Case series

A retrospective study was conducted on a total of 105 cases of thyroid papillary microcarcinoma ("occult" or "incidental") to identify a spectrum of morphological changes from benign reactive thyroid follicles to potential intrafollicular neoplasia (TIN). Microcarcinoma was found in association with multinodular goiter (52%), chronic thyroiditis (19%), follicular adenoma (19%), parathyroid neoplasia (5%), and no evident thyroid pathology (5%).

Results

In our case series, multinodular goiter was the most frequent thyroid pathology associated with "occult" or "incidental" papillary microcarcinoma (52%).

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TABLE I – Related thyroid pathologies in patients with occult papillary carcinoma

• Multinodular goiter	54 (52%)
• Chronic thyroiditis	19 (18%)
• Follicular adenoma	19 (18%)
• Parathyroid neoplasia	6 (5%)
• Others	6 (5%)

a) *Histological aspects of thyroid papillary microcarcinoma (PTMC):*

The earliest recognizable cellular atypia consists of small single follicles with an irregular shape and characteristic dysmetric nuclei with a fine chromatin pattern, chromatin clearing, grooves of nuclear membrane and intranuclear inclusions. Atypical follicles were found isolated or in small clusters, in an apparently normal thyroid parenchyma, frequently associated with lymphoid nodular reactive infiltrates.

Stromal sclerosis appeared to be a secondary phenomenon, revealing a tubular pattern of atrophic follicles, cellular polystratification and papilla budding, with a fine fibrovascular

stroma and microcalcifications. The follicle pattern and nuclear abnormality could be identified as mild, moderate or severe follicular dysplasia and might be a marker for the purposes of histological and cytological diagnosis.

In our experience, a suspect lymph node detected at thyroidectomy for multinodular goiter was found to be metastatic, with “occult” thyroid carcinoma in 5-10% of cases. The primary tumor was a microcarcinoma less than 6 mm in size and was frequently located at the superior pole of the right lobe. In one patient, the microcarcinoma was only 1.5 mm in diameter and was located near the capsule of the thyroid in a V-shaped intraparenchymal sclerotic area (Fig. 1). In this case, the histological pattern is not papillary, but the so-called follicular variant, represented by elongated microfollicles that have no colloid substance and are characterized by the well-known nuclear atypia, such as a fine chromatin pattern, chromatin clearing, longitudinal grooves, an irregular nuclear membrane, intranuclear inclusions and epithelial budding (Fig. 2). Single atypical follicles can infiltrate the fibrous tissue of the adjacent thyroid capsule (Fig. 3) and may be an early



Fig. 1: Histology of a case of PTMC 1.5 mm in diameter in a V-shaped subcapsular parenchymal sclerotic area. (H&E) x10).

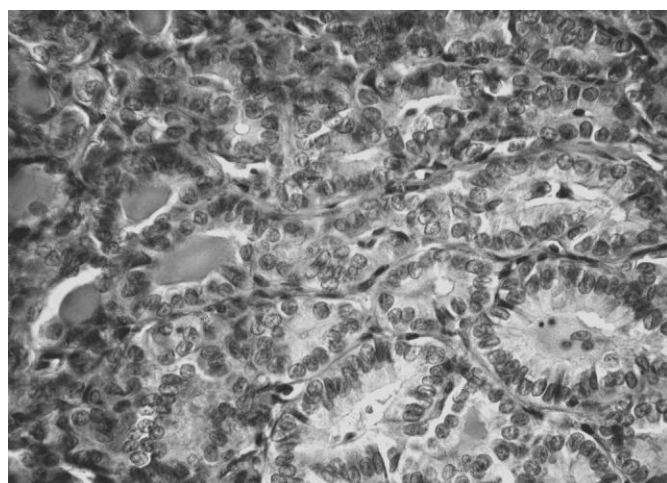


Fig. 2: High magnification shows no papillary pattern, but elongated microfollicles with epithelial nuclear atypia, e.g. chromatin clearing, longitudinal grooves and intranuclear inclusions. (H&E) x40).

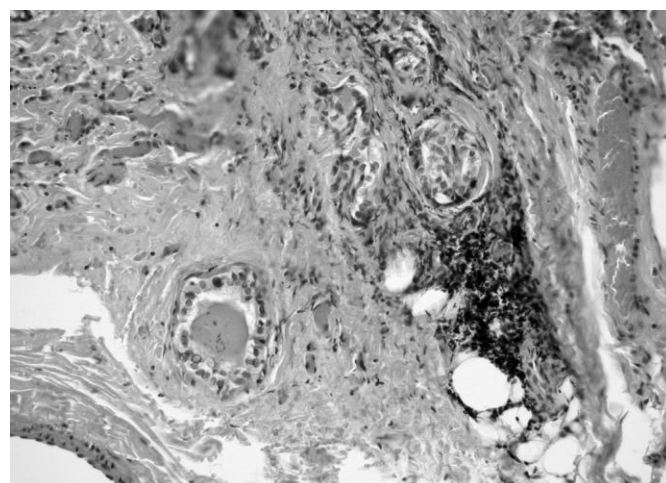
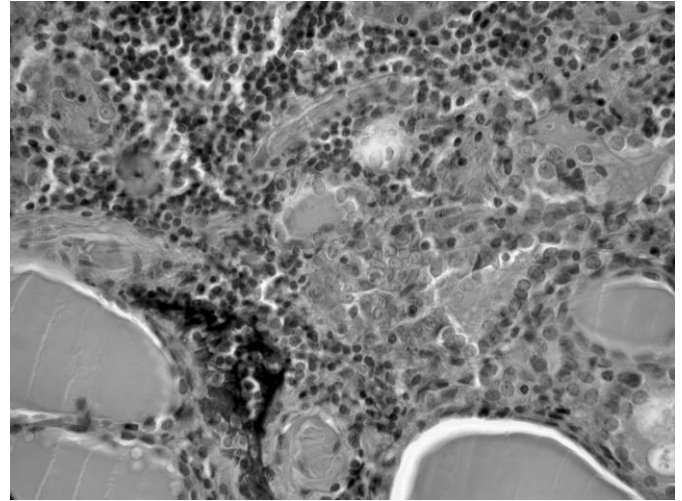
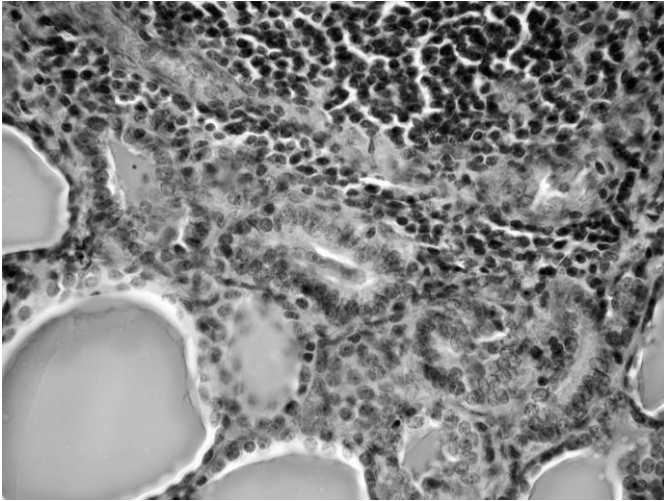
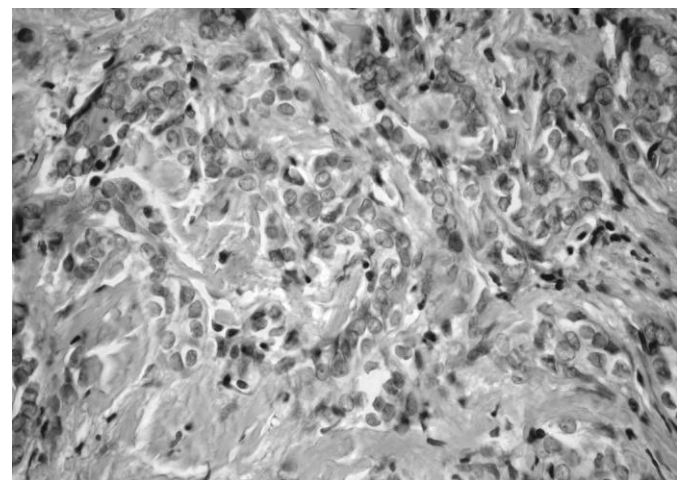
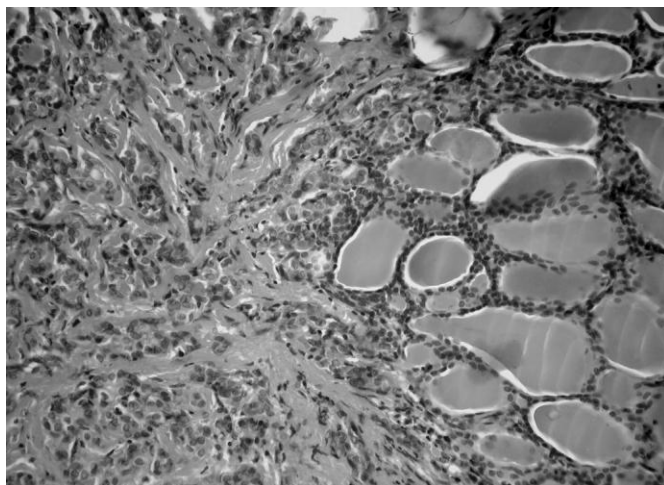


Fig. 3: Thyroid fibrous capsule thickened and infiltrated by small neoplastic follicles. (H&E) x 40).



Figs. 4-5: Low-grade thyroid intrafollicular neoplasia (TIN-LG). Small follicles without colloid are surrounded by crowded multilayered cells and epithelial budding with rather vesicular, large nuclei that also have a thick and irregular nuclear membrane. Note the presence of a focus of inflammatory reactive lymphoid infiltration. (H&E x40).



Figs. 6-7: High-grade dysplastic intrafollicular lesion (TIN-HG). The nuclear chromatin dispersion and grooves are associated with an increase in the collagen interfollicular stroma (va un punto dopo collagen?) characteristic of papillary carcinoma (H&E x40).

step in a more dangerous stage, even in the case of very small papillary microcarcinoma.

b) Epithelial follicular changes in the marginal zone of the PTMC

Areas of thyroid surrounding an unencapsulated neoplasm reveal atypical follicles, characterized by small size, variable shape and a narrow lumen with no colloid, near reactive inflammatory lymphoid nodules. These follicles are surrounded by crowded, multilayered cells with rather vesicular, large nuclei that also have a thick and irregular nuclear membrane (Figs. 4, 5). These features can be considered as a low-grade intrafollicular epithelial dysplasia, as described in CIN 1 or low-grade SIL of the uterine cervix, or low-grade PIN in the prostate. The presence of chromatin dispersion and longitudinal nuclear

grooves can be interpreted as a morphological sign of a high-grade dysplastic intrafollicular lesion, associated with dense collagen interfollicular stroma, which is a precursor of a papillary carcinoma (Figs. 6, 7). Such signs can act as morphological markers of a multicentric thyroid tumorigenesis, rather than intraglandular micrometastasis.

c) Abnormal follicles and nuclear atypia in Hashimoto's thyroiditis

Various abnormal follicles and nuclear epithelial atypia can be observed in Hashimoto's thyroiditis too, by either fine needle aspiration cytology or histology. These aspects should not be confused with intrafollicular dysplastic lesions, however, since they are hyperplastic, benign, oncocytic nodules (or Hurthle cells) (Fig. 8).

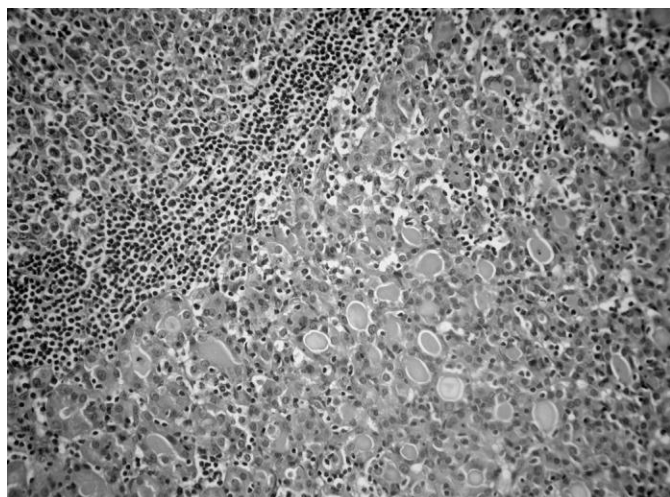


Fig.8: Abnormal follicles and nuclear atypia in a hyperplastic benign oncocytic nodule (H&E x25).



Fig. 9, 10: PTMC arising in encapsulated follicular neoplasia (H&E x10 x25).

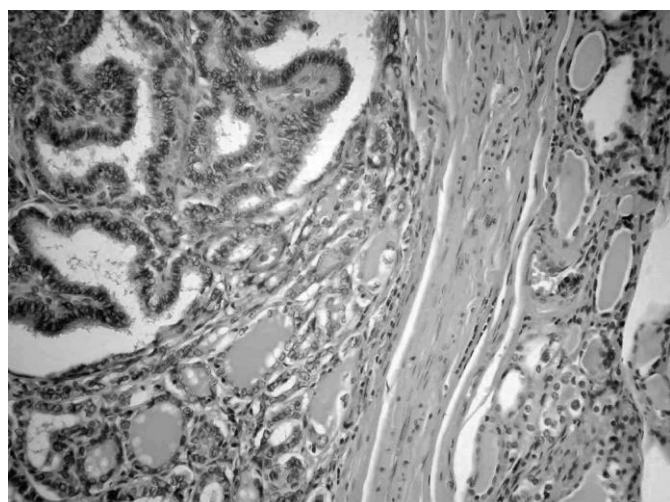


Fig. 10.

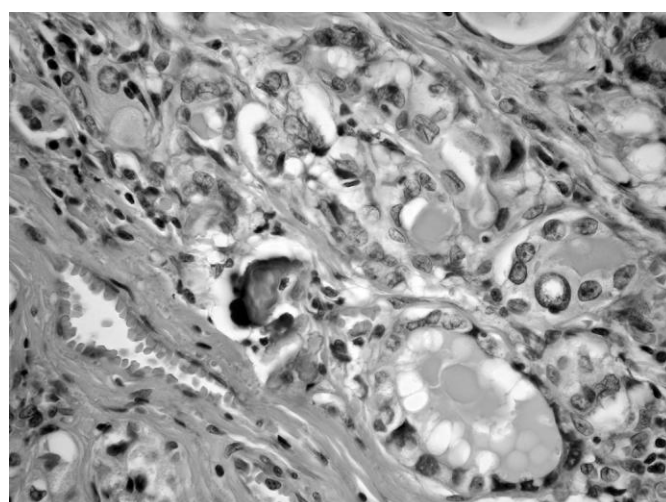


Fig. 11: Note the atypical nuclear changes in the neoplastic cells surrounding a fibrovascular stroma (H&E x 40).

d) Papillary microcarcinoma and follicular neoplasia

Papillary microcarcinoma may be associated with an encapsulated follicular neoplasia (Fig. 9). It is worth noting the atypical nuclear features of the carcinoma (overlapping nuclei with clear chromatin, presence of grooves, etc.), associated with proliferating fibrous stroma (Fig. 10). The thyroid follicles show obviously atypical features (nuclear asymmetry, irregular chromatin, which is clear and dense, etc.) that are characteristic of a mixed follicular-papillary neoplasm and of the follicular variant of papillary carcinoma (Fig. 11).

Discussion

Papillary microcarcinoma is usually diagnosed during or after surgery, but may also be detected at autopsy. In

recent years, high-resolution ultrasound imaging combined with FNAC have been routinely used to assess subjects at risk and enable the early detection of thyroid carcinomas less than 1 cm in diameter (microcarcinoma according to the WHO). ECO-FNAC screening is recommended for people exposed to radiation or with a positive family history of thyroid cancer, multinodular goiter, chronic thyroiditis, Graves' disease, thyroid adenoma, laterocervical lymph node metastasis, and hyperparathyroidism.

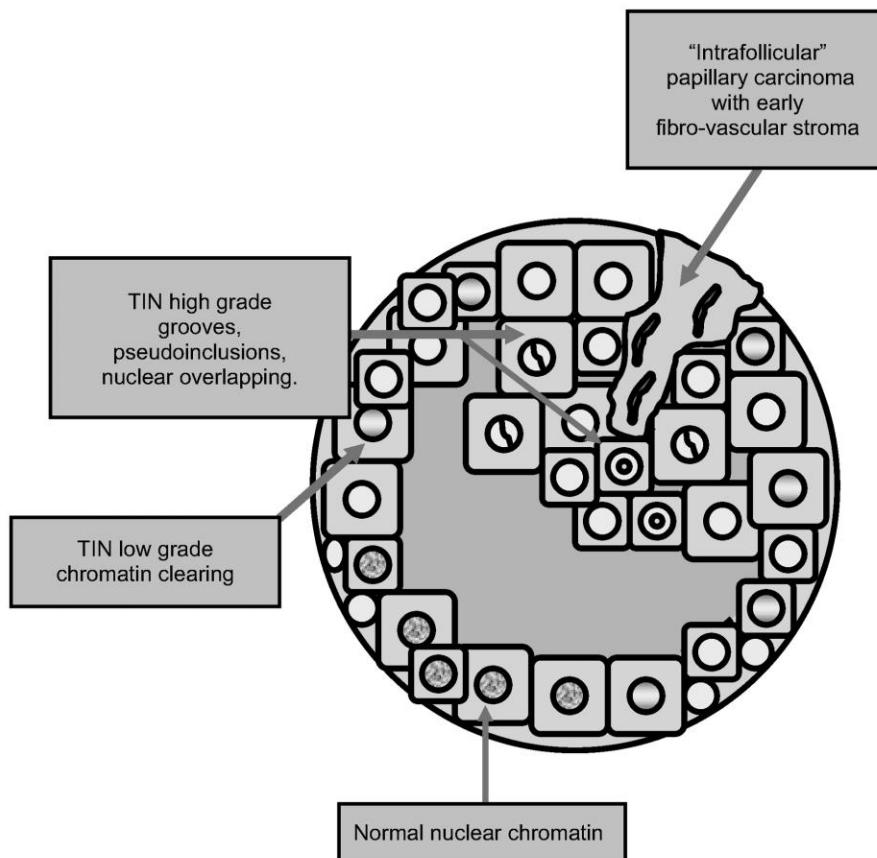
Thyroid microcarcinoma has been observed more frequently by clinicians in recent years and poses another crucial cytological diagnostic problem and therapeutic dilemma. We believe that the morphological definition of some nuclear atypia, a precursor of malignancy, would help pathologists to clarify their reporting not only of *microcarcinoma*, but also – in diagnostic FNAC proce-

dures - of so-called "follicular neoplasia", or "suspected follicular variant of papillary carcinoma", or "atypia in thyroiditis", etc.

Low-grade and high-grade thyroid intrafollicular neoplasia (TIN) could represent a cytological marker of dysplastic lesions and precursors of thyroid carcinoma still in an early intrafollicular or pre-invasive stage in various pathological processes of the thyroid. Further molecular studies to identify any met/HGF protein overexpression or ret/PTC oncogene rearrangements may be useful in providing additional prognostic factors for microcarcinoma and/or occult thyroid carcinoma (OTC) and thyroid intrafollicular neoplasia (TIN).

The atypical features of follicular epithelial areas can vary widely, starting with a non-specific dispersion of nuclear chromatin. This can spread, leading to chromatin clearing and irregularities in the nuclear membrane (low-grade TIN). It is worth noting the formation of longitudinal grooves and nuclear inclusions (high-grade TIN). Then epithelial intrafollicular budding occurs, along with the formation of papillary microcarcinoma with thin fibrovascular axes. These morphological changes are histological and cytological markers of an abnormally reactive follicle, giving rise to the so-called low-grade and high-grade TIN.

TABLE II – Schematic illustration of the process of tumorigenesis in thyroid follicles



Riassunto

SCOPO DELLO NOSTRO STUDIO: Identificare in varie condizioni patologiche della tiroide uno spettro di alterazioni morfologiche degli epiteli dei follicoli tiroidei riferibili o a processi reattivi di natura benigna o ad alterazioni displastiche di vario grado degli epiteli follicolari quali possibili precursori morfologici del microcarcinoma papillare della tiroide.

CASISTICA: Si riferisce ad uno studio retrospettivo di un totale di 105 casi in cui il microcarcinoma papillare occulto o incidentale della tiroide era associato ad un gozzo multinodulare (52%), ad una tiroidite cronica (19%), ad un adenoma follicolare (19%), ad una neoplasia della paratiroide (5%) ad anche senza patologia tiroidea evidente (5%).

RISULTATI: Follicoli atipici di vario grado vengono descritti in relazione alla presenza di infiltrati infiammatori, sclero-

rosi dello stroma tiroideo, noduli proliferativi degli epitelii follicolari sia di natura iperplastica che adenomatosa. L'aspetto istologico del carcinoma papillare viene confrontato con le alterazioni morfologiche osservate in follicoli atrofici e/o reattivi e viene inoltre identificata una progressiva alterazione degli epitelii dei follicoli fino all'identificazione di una cosiddetta neoplasia tiroidea intrafollicolare (TIN di basso o alto grado) quale precursore morfologico del carcinoma papillare della tiroide.

CONCLUSIONI: Le caratteristiche atipiche degli epitelii follicolari iniziano con una dispersione della cromatina nucleare a cui segue un'alterazione del profilo della membrana nucleare che appare ispessita, a decorso irregolare e incisa sino alla presenza di pseudoinclusi nucleari e alla comparsa di micropapille per la proliferazione di sottili assi connettivo-vascolari. La valutazione in gradi (lieve o alto) della neoplasia tiroidea intrafollicolare (TIN) potrebbe rappresentare un test citologico per identificare lesioni displastiche e precursori del carcinoma tiroideo papillare nell'ambito di vari processi patologici della tiroide.

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