sciendo Acta Medica Marisiensis 2018;64(3):121-125 DOI: 10.2478/amma-2018-0015

CASE REPORT

Histopathological Diagnostic Criteria for Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features Highlighted by Six Illustrative Cases

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Introduction. The encapsulated, non-invasive subtype of follicular variant of papillary thyroid carcinoma (FVPTC) represents approximately 10% to 20% of all thyroid cancers. Many studies over the past decade have shown that these tumors carry an indolent clinical course, with no recurrence, even in patients treated by lobectomy. Their reclassification as neoplasms with "very low malignant potential" has recently been suggested by an international group of experts and a new terminology was proposed: "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). However, a diagnosis of NIFTP is still challenging for many pathologists in daily practice. **Presentation of case series**. By presenting six illustrative cases of NIFTP, this article aims to highlight the diagnostic criteria and the burden difficulties when dealing with NIFTP cases. Characteristic histological features, inclusion and exclusion criteria for NIFTP, as well as sampling guidelines and differential diagnosis challenges are all discussed. **Conclusions**. The diagnosis of NIFTP is not straightforward and requires meeting strict inclusion and exclusion criteria. Total sampling of the tumor capsule in these cases is mandatory in order to exclude invasion (capsular and/or vascular). A diagnosis of NIFTP promotes a less-aggressive patient management that is, no need for completion thyroidectomy or radioactive iodine therapy.

Keywords: NIFTP, thyroid neoplasm, papillary thyroid carcinoma

Received 11 June 2018 / Accepted 25 July 2018

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, with a significant increasing incidence in the last four decades [1]. According to the growth pattern, two types of PTC are described: "conventional" PTC in which the architecture is manly papillary or mixed papillary and follicular, and the "follicular variant" of PTC (FVPTC) with a follicular growth pattern. This last variant was first described by Linsday in 1960 as a tumor with nuclear characteristics similar to those of PTC, a follicular growth pattern and a propensity for lymphatic and hematogenous spread similarly to PTC. Later on, it has been recognized that FVPTC has two distinct subtypes: encapsulated and infiltrative according to the presence/absence of encapsulation [2]. These 2 subtypes have clinically and genetically distinct characteristics [3-6]. Until recently, encapsulated FVPTCs were further classified into non-invasive and invasive subtypes according to the presence of tumor capsular or vascular invasion [6,7].

Many studies over the past decade have shown that non-invasive encapsulated FVPTCs carry an indolent clinical course and are not associated with tumor recurrence even in patients treated by lobectomy only [2,3,6-10]. Considering these, reclassification of non-invasive encapsulated FVPTC as a neoplasm with "very low malignant potential" has recently been suggested by an international group of specialists in thyroid pathology. A new terminology was proposed: "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) [11]. NIFTP is now considered a distinct category and was also included in the new WHO (World Health Organization) Classification of *Tumors of Endocrine Organs* 2017 [12]. The introduction of NIFTP represents a significant paradigm shift in thyroid pathology and is thought to have a major impact in the diagnosis and treatment of thyroid neoplasms [13].

However, a diagnosis of NIFTP is still challenging for many pathologists in daily practice. By presenting six illustrative cases of NIFTP, this article aims to highlights the diagnostic criteria and the difficulties when dealing with NIFTP cases. Characteristic histological features, inclusion and exclusion criteria for NIFTP, as well as sampling guidelines and differential diagnosis challenges are all discussed.

Presentation of case series

Patients

All the cases included in the study were retrieved from the files of the Department of Pathology, Tîrgu-Mureş County Hospital, between May 2016 and February 2018.

Written informed consent was obtained from all patients included in this study. The Ethics Committee of the University of Medicine and Pharmacy of Tîrgu-Mureş approved the study.

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Table I. Demographical and pathological characteristics for the study cases.

	Age/ Sex	Extent/ type of surgery	Tumor location	Microscopical features							
				Tumor size (mm)	Multi-focality	Encapsulation/ well demarcation	Capsular ±vascular invasion	Growth pattern (predominat)	Other growth patterns (%)	Intra-tumoral fibrosis	Nuclear score*
Case no. 1	42/F	TT	LTL	17	no	well demarcated by thin or partial capsule	absent	microfolicular	solid (20%)	absent	3
Case no. 2	38/F	TT	LTL	20	no	encapsulated, thick capsule	absent	microfolicular	-	absent	2
Case no. 3	31/F	LL	LTL	20	no	encapsulated, thick capsule	absent	microfolicular	solid/trabecular (20%)	present	2
Case no. 4	41/F	TT	LTL	27	no	well demarcated by a thin or partial capsule	absent	micro- and normofolicular	solid (20%)	absent	2
Case no. 5	27/F	LL	LTL	11	no	well demarcated by a thin or partial capsule	absent	microfolicular	solid (20%)	present	3
Case no. 6	48/F	TT	LTL	15	no	well demarcated by a thin or partial capsule	absent	microfolicular	trabecular/ solid (20%)	present	2

Legend Table I: TT: Total Thyroidectomy; LL: Left lobectomy; LTL: Left Thyroid Lobe.

*Score 2: evidence of at least two of the following characteristic nuclear features: (1) size and shape (enlargement/overlapping/ crowding, elongation), (2) membrane irregularities (irregular contourus, grooves, pseudoinclusions) and (3) chromatin characteristics (clearing and margination/glassy nuclei). Score 3: evidence of all three nuclear features categories mentioned above.

Demographical and pathological characteristics for the study cases are summarized in Table I.

Results

All patients were females, aged between 27 to 48 years-old, who had been admitted to hospital for a cold, hypoechoic, solitary thyroid nodule. Four cases involved total thyrodectomy; in the other two cases, left lobectomy was performed. Tissue samples were sent to the Department of Pathology.

Histopathological analysis of the tissue samples

The surgical specimens were all fixed in 10% buffered formaldehyde for between 48 to 72 hours, depending on the size of the specimen. The tumors were entirely sampled and further processed according to routine practice guidelines, which included dehydration, clearing and paraffin embedding.

Five-µm-thick sections were stained with hematoxylin-eozine (HE) and examined by two pathologists (ANB, AB), independently and then together by a double-headed microscope.

Pathological features (Table I)

In all cases, a well-delimited, solitary, compact, gray-whitish nodule was described, with a maximal diameter ranging between 11 to 27 mm.

In two cases, the nodules were clearly encapsulated, with evidence of a thick, calcified capsule surrounding the nodule (Figure 1A). In the other four cases encapsulation was described as being very thin or partial capsule (Figure 1B). In all six cases, however, there was a sharp interface between the tumor and remaining parenchyma. No signs of capsular or vascular invasion were observed following sampling of the entire tumor nodules and multiple sections evaluation. The predominant architectural pattern was micro-follicular (Figure 1C). In five cases solid, trabecular growth patterns were also present (Figure 1D), but represented less than 30% of the tumor area. The nuclei revealed discrete, incomplete characteristic of PTC nuclear features. They were minimally to moderately enlarged with nuclear membrane irregularities, including groves or indentations, or nuclear clearing.

Three cases met two of the three nuclear criteria, and the remaining three met all three nuclear criteria for NIFTP (Figure 2A, B) (Figure 2C, D).

All cases were consistent with a diagnosis of "non-invasive follicular thyroid neoplasm with papillary-like nuclear features", based on the following criteria, in accordance with Nikiforov et al. (11):

- encapsulation/ well demarcation of the tumor's interface from the adjacent thyroid parenchyma.
- absence of invasion (capsular and/or vascular) following entire sampling of the tumor capsule and multiple sections evaluation.
- dense, microfollicular growth pattern of the tumor, with the solid growth component, if present, represented less than 30%.
- focal characteristic PTC nuclear changes, alternating with areas in which the nuclear changes were only discrete and incomplete and a nuclear score of 2-3.

Discussion

The encapsulated, non-invasive subtype of FVPTC accounts for up for 10% to 20% of all thyroid cancers in Europe and North America [14].

In 2016 a new terminology for these tumors was proposed by Nikiforov et al. (11) who suggested they be reclassified as neoplasms with "very low malignant potential". Clinically, this reclassification is expected to have many consequences including a decrease in the number of PTCs, a decrease in complications due to total thyroidectomy or RAI, a reduction in medical expenses and a significant reduction in the psychological and social stress associated with the word "cancer" on patients.

However, it is essential that the diagnosis of NIFTP, as detailed by Nikiforov et al. [11] is determined accurately, as this will dictate a different therapeutic approach compared to PTC or other types of thyroid cancer [15].

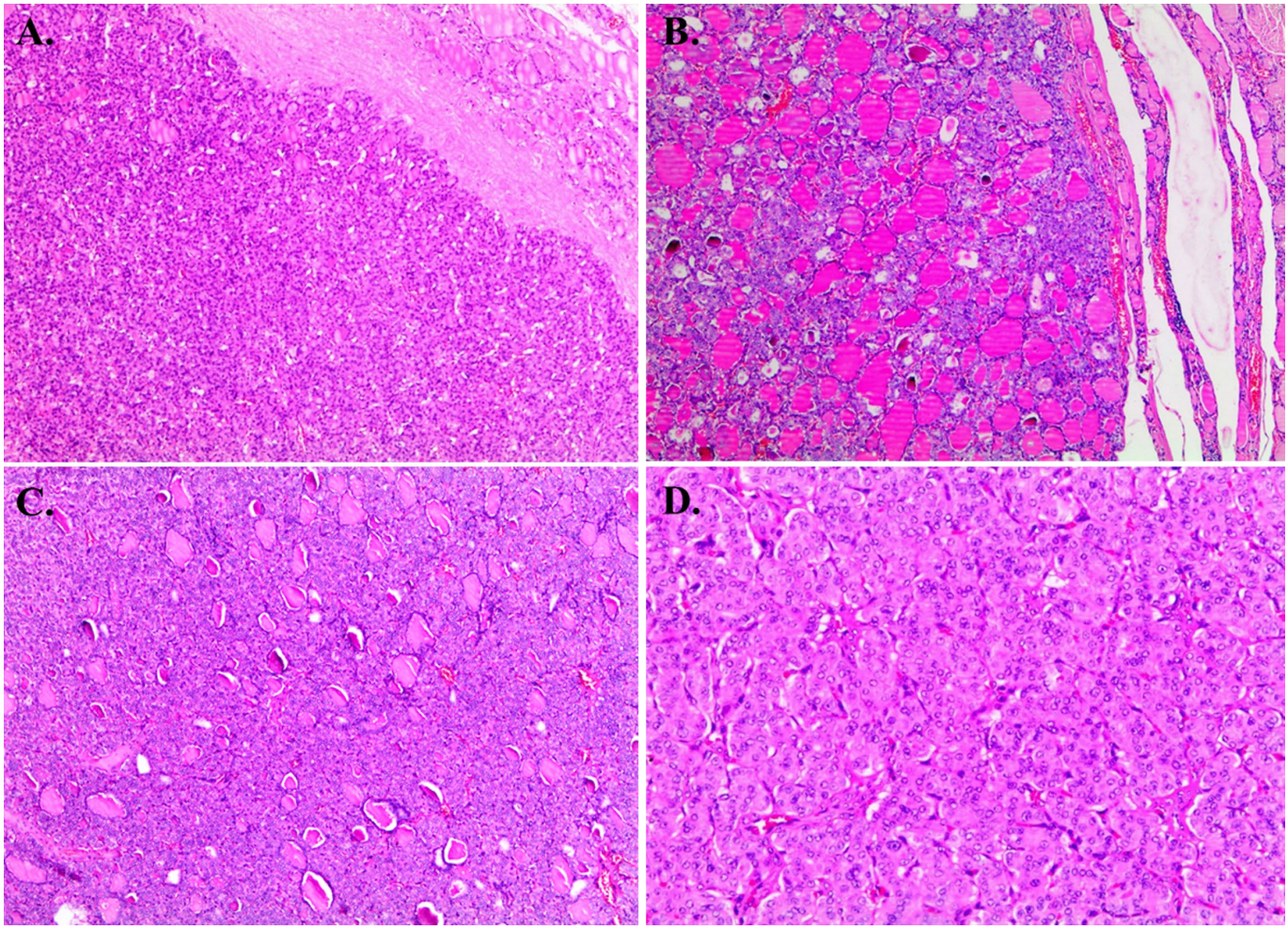

Fig. 1. Diagnostic criteria for non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): encapsulation (A, 4x) or clear demarcation by a very thin, partial capsule (B, 4x) with no signs of capsular or vascular invasion; follicular architecture with a predominant microfollicular growth pattern and no papillae (C, 4x); solid, trabecular growth patterns can also be present, but these areas should represent less than 30% of the tumor (D, 10x).

Tumors designated as NIFTP are required to meet strict inclusion and exclusion criteria.

Inclusion criteria are:

– size of the tumor more than 1 cm, with encapsulation or clear demarcation.
– follicular growth pattern.
– a nuclear score 2-3.

Nikiforov et al. developed a simple and reproducible nuclear scoring system that could assist in the diagnosis of NIFTP in every-day practice [11]. The characteristic PTC nuclear features were separated into three main categories: (1) size and shape (enlargement/overlapping/crowding, elongation), (2) membrane irregularities (irregular contours, grooves, pseudoinclusions) and (3) chromatin characteristics (clearing and margination/glassy nuclei). Each class of nuclear features was given a score of 0 or 1 resulting in a range of scores from 0 to 3.

In our series, three cases were consistent with a nuclear score of 2, and three cases fulfilled all criteria and were consistent with a nuclear score of 3.

Exclusion criteria are:

– true papillae >1%. (2)
– psammoma bodies.
– capsular or vascular invasion.
– tumor necrosis.
– high mitotic activity.
– >30% solid/trabecular/insular growth pattern.
– size of the tumor ≤1 cm.

By applying these criteria conventional PTC (true papillae >1% and psammoma bodies), invasive subtype of encapsulated FVPTC (capsular and/or vascular invasion) and poorly differentiated thyroid carcinoma (tumor necrosis and high mitotic activity) are excluded [16].

Since previous studies have evaluated only tumors larger than 1 cm, tumors below 1 cm should not be classified as NIFTPs, but as papillary thyroid micro-carcinomas. Addressing issues of diagnosis, a recent monograph [17] provides a synopsis and guide for pathologists on NIFTP and focuses on histologic features, including inclusion and exclusion criteria used to define NIFTP, as well as grossing guidelines, reporting practices, and potential diagnostic limitations.

Conclusions

The introduction of the terminology NIFTP represents a significant paradigm shift in thyroid pathology. Herein, we

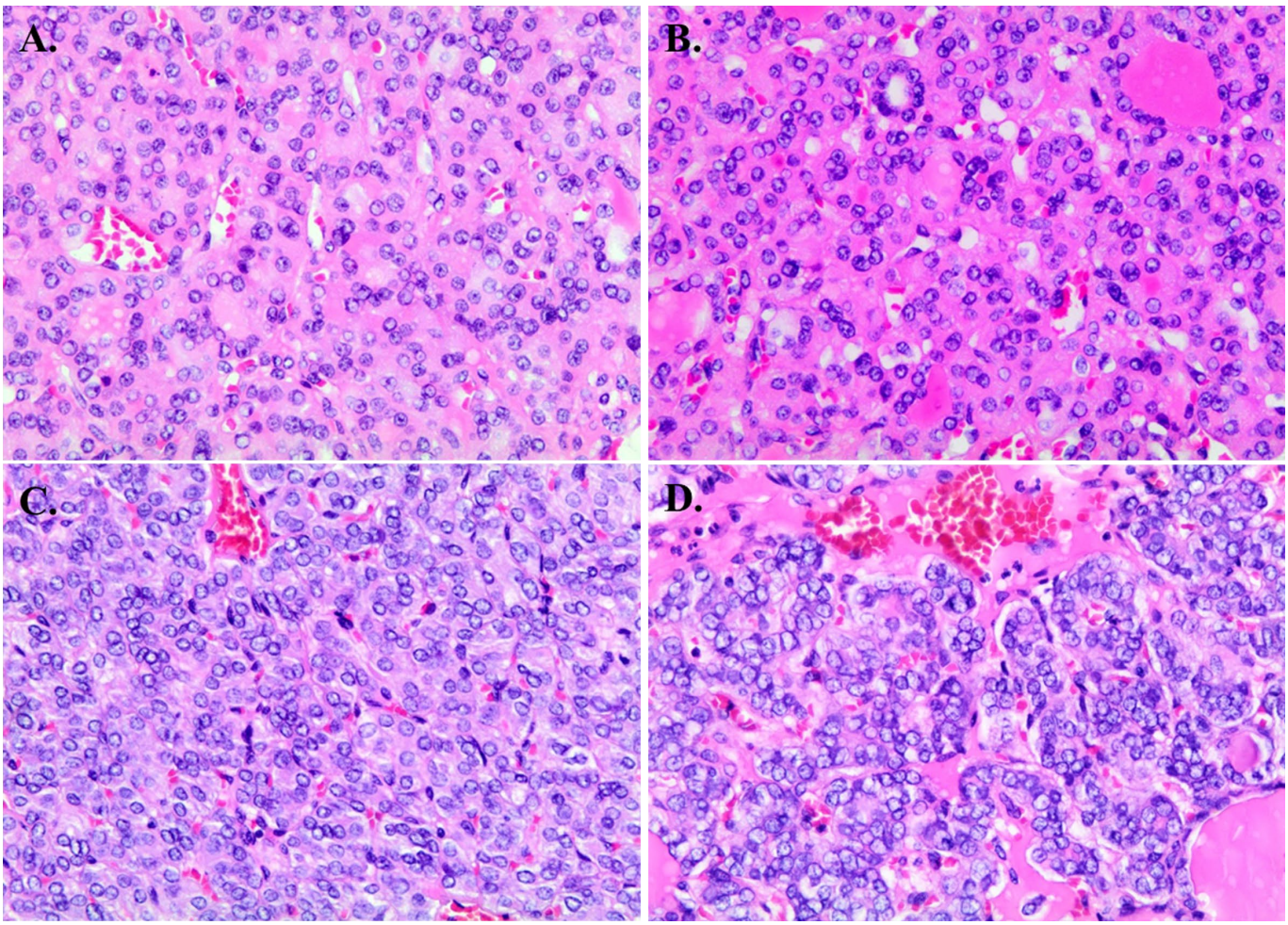

Fig. 2. Nuclear features of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). A nuclear scoring system can be utilized in evaluating NIFTP. Nuclear features are grouped in three categories (1) size and shape (enlargement/overlapping/ crowding, elongation); (2) membrane irregularities (irregular contourus, grooves, pseudoinclusions) and (3) chromatin characteristics (clearing and margination/glassy nuclei). For each feature, a tumour can receive one point, such that a tumour can score a total of 0-3 points. Eg: a tumour consisting with score 2 (A, B, 40x) and a tumour consisting with score 3 (C, D, 40x).

report the first six cases of NIFTPs diagnosed in our department since the introduction of the new terminology. Labeling these lesions as tumors, rather than carcinomas reflects more accurately their biologic potential and promotes less-aggressive patient management. It follows that there is no need for completion thyroidectomy or radioactive iodine therapy.

However, the term NIFTP has been proposed for lesions meeting strict inclusion and exclusion diagnostic criteria. Total sampling of the tumor capsule in these cases is mandatory in order to exclude capsular or vascular invasion.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

This work was supported by the University of Medicine and Pharmacy of Tîrgu-Mureş Research Grant No. 275/1/11.01.2017.

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