Mini Review

Non-invasive Follicular Tumour with Papillary-Like Nuclear Features (NIFTP) – Is It Like a Tiger in a Cage?

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Abstract

Context: This is an article which presents a review of non-invasive follicular tumour with papillary like nuclear features (NIFTP). It includes its current definition and histopathological characteristics. The article differentiates NIFTP from follicular variant of papillary carcinoma thyroid. **Objectives:** This article emphasises on the diagnostic features of NIFTP. It discusses its histopathological features, molecular profile and the importance of grossing the capsule to exclude the diagnosis of carcinoma. The article focuses on the problems which are usually associated with the diagnosis and management of NIFTP. **Data sources:** Review of articles on NIFTP and articles focusing on differences between NIFTP and papillary carcinoma thyroid. **Conclusion:** NIFTP is a low risk indolent neoplasm which when diagnosed using appropriate histopathological criteria are not associated with metastatic or recurrent diseases at least for intermediate period of follow up. The article differentiates between true neoplastic papillae and hyperplastic or degenerative papillae and how does it affects the diagnosis of NIFTP. It also discusses cytological features, micro NIFTP and features of the neoplasm which are still to be studied, which may affect the outcome of the disease.

Keywords: NIFTP; FVPTC; Disease

Introduction

Papillary Thyroid Carcinoma (follicular variant) (FVPTC) and Non – Invasive Follicular Carcinoma (with papillary-like nuclear features) (NIFTP) have been the bane of histopathological diagnosis everywhere and have caused much consternation around the reporting rooms of the world. Questions regarding their management and indications for lobectomy or thyroidectomy remain largely unanswered.

Papillary Thyroid Carcinoma (follicular variant) (FVPTC)

The FVPTC can be divided into two types, encapsulated (EFVPTC) and non-encapsulated. EFVPTC can show capsular invasion and vascular invasion. EFVPTC is further classified into encapsulated invasive and encapsulated non-invasive forms [1]. Extensive revaluation of EFVPTC was done by a panel of international experts in 2016 which showed that encapsulated non-invasive FVPTC with specific histopathological characteristics in the follow up study of 13 years (median) had an extremely indolent behaviour [2]. In order to emphasise the indolent nature of the disease the word carcinoma was removed from this terminology to downscale the treatment approach [2].

It was in 2017 that the IVth edition of the WHO classification of tumours of endocrine organs, replaced the term noninvasive EFVPTC with the term NonInvasive Follicular Carcinoma with papillary-like nuclear features (NIFTP).

Number of studies conducted have confirmed that the prognosis depends on invasiveness or non-invasiveness of this tumour [3-5]. Thus, the concept which developed was that NIFTP has very good prognosis and very low risk of metastasis. Therefore, if they are non-invasive and non-metastatic, they do not require total thyroidectomy and can be managed with lobectomy [6].

Non–Invasive Follicular Carcinoma (with papillary-like nuclear features) (NIFTP)

Is NIFTP a benign neoplasm? The lay press concluded these tumours as benign but they have never been called benign by the pathologists involved in the original study rather NIFTP is considered as preinvasive. They can be compared to "a tiger in a cage" similar to situ ductal carcinoma of the breast.

Few cases diagnosed as NIFTP did present with nodal metastases but the diagnostic criteria have since evolved and become much more robust [7].

Histopathological criteria for diagnosis of NIFTP

- They are well circumscribed, encapsulated tumours without any evidence of invasion (capsular /vascular). Infiltration into the surrounding thyroid is the term reserved for unencapsulated tumours [1].
- These tumours with follicular growth pattern do not show true papillae (True papillae can be defined as complex, arborizing papillae with fibrovascular core or in simple words fibrovascular core lined by 1 or 2 layers of epithelium).
- Factors like incomplete or absent core, geographic linearity,

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haemorrhage, hemosiderin, inflammation, vascular proliferation and metaplasia favours FNAC/biopsy created papillae. Thus, the presence of true papillae favours the diagnosis of papillary carcinoma whereas hyperplastic or degenerative papillae favours NIFTP.

- Psammoma body is formed due to dystrophic calcification of true papillae in papillary carcinoma thyroid. Presence of psammoma bodies favours PTC and goes against the diagnosis of NIFTP.
- Presence of >30% solid growth rules out NIFTP according to original definition. However, in some NIFTPs (>3.5 cm) focus of tiny microfollicular growth may be seen. It is only a small fraction of the entire tumour and does not exclude diagnosis of NIFTP.
- Necrosis or any abnormal mitotic figures are not observed in NIFTP. More than 3 mitoses per 10 high power field is bothersome and the pathologist should then be very cautious in making the diagnosis of NIFTP.
- Necrosis can be seen in the area where FNAC was performed but this necrosis is infarct like. On the other hand, coagulative necrosis, if present, favours high grade carcinoma.
- Nuclear characteristics of NIFTP are same as that of papillary carcinoma thyroid, with the nuclear score of 2-3. The revised diagnostic criteria say that if the nuclear score is three then careful revision of whole tumour is recommended to exclude the presence of papillae.

Morphological characteristics of other variants of PTC, such as tall cell, cribriform – morular and solid / trabecular variants are not recognised in NIFTP.

Evaluation of Tumour Capsule / Grossing

Grossing of the tumour capsule is critical for the diagnosis of NIFTP [2]. To address this issue, the entire tumour capsule or tumour normal interface should be submitted for histopathological examination. Seethala et al has proposed the protocol for tumour sampling. For large lesions, stepwise submission of sections is recommended which includes limited generous sampling initially followed by submission of remaining tumour capsule if no capsular or vascular invasion is detected initially.

In the modified transverse vertical gross examination method additional vertical cuts are done at the upper and lower ends of thyroid nodules. This method was found to be more effective for detecting capsular invasion.

Cytology of NIFTP

There are well defined validated cytomorphological criteria to differentiate most benign and malignant nodules. However, follicular patterned tumours like NIFTP, follicular patterned adenomatoid nodule or follicular adenoma cannot be distinguished on cytology alone .

The NIFTP can be classified into any of the three Bethesda categories, namely III(AUS), IV (follicular neoplasm) or V (suspicious for papillary thyroid carcinoma) but as NIFTP is an indolent tumour, the risk of malignancy of these Bethesda categories decreases.

The cytological features such as microfollicular growth pattern, absence of papillary structures and lack of well-formed pseudoinclusions can help in the preoperative diagnosis of NIFTP.

There are other authors who do not rely on these cytomorphological characteristics alone. They have shown that cytological features along with radiological features and molecular features together may prove to be more effective for preoperative diagnosis of NIFTP.

Micro –NIFTP

NIFTP which are less than 1cm in diameter are called as micro NIFTP. Earlier studies did not include micro NIFTP [26] but now the studies on these subcentimetric lesions confirm that they behave in very low risk manner and can be diagnosed as micro NIFTP.

Molecular Profile of NIFTP

Mutations of thyroid cancer involve about 7 genes. The mutation in these genes are mostly mutually exclusive. Mutation in BRAF, RET and TRK genes are found in papillary carcinoma thyroid. N-RAS is seen in FVPTC. PAX-8/PPAR-gamma is associated with FNs.H-RAS and K-RAS are commonly seen in FNs than in papillary carcinoma thyroid.

These seven genes are seen at the initiation of thyroid follicular cancer, following which they are complicated by multiple point mutations in RAS and BRAF genes and many different translocations of RET and TRK.

About 78% of NIFTP cases show molecular changes. About 30% to 54% of cases show RAS mutations with NRAS being most common and KRAS being rare. But detection of NRAS is also not specific as it may also be seen in follicular carcinoma and invasive encapsulated FVPC. Few cases of NIFTP also show PPARG fusion, THADA fusions and BRAF K601E. This rare BRAF mutation is regarded as RAS-like as it is seen in follicular neoplasms. Its association with indolent behaviour in noninvasive tumors and its mechanism of activation of MAPK and PI3K signalling pathways are clearly different from BRAFV600E mutated tumors.

There are some studies which have shown miRNA expression in NIFTP cases and have found that miR-10a05p and MiR-320e can distinguish between NIFTP and IFVPCT.

Conclusion

NIFTP is a relatively new entity. It is a thyroid follicular neoplasm which has very low to intermediate risk of malignancy. The inclusion of this category has reduced the incidence of overdiagnosis of thyroid carcinoma.

High index of diagnostic suspicion by the pathologist for NIFTP and appropriate management like lobectomy by the clinician are absolutely vital for the patient. Multifocal and oncocytic NIFTP need further evidence. Much longer follow up studies are the need of the hour for long term prognostic implications and to rule out the possibility of metastasis in these tumors.

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