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A wolf in NIFTP's clothing

Molecular pathology settles NIFTP versus papillary carcinoma and personalises care

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FNA
Thy5

SURGERY
Thyroidectomy

H&E
Encapsulated, trabecular, microfollicular

OPINION DIVIDED
NIFTP or PTC?

IHC
BRAF V600E (VE1) positive

NGS
BRAF V600E + TERT C250T

DIAGNOSIS
PTC: personalised plan

Background

- Papillary thyroid carcinoma (PTC) accounts for nearly 90% of thyroid cancers and is the commonest endocrine malignancy [1,2]. Standard of care is resection + radioactive iodine (RAI) as first-line [3].
- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was distinguished from PTC in 2016, as an indolent neoplasm adequately treated by lobectomy surgical resection alone [4].
- This is a case of a histomorphologically ambiguous lesion, which led to the use of molecular testing to reach a diagnosis.

Case presentation

- A 54-year-old man presenting with six weeks of hoarseness and an ill-defined right neck lump led to a suspected cancer referral to ENT.
- A U3, Thy5 right lobe nodule was found on ultrasound and cytology.
- Discussed at local head and neck, and specialist thyroid MDTs. Planned management was total thyroidectomy then radioactive iodine (RAI).

Radiology

- **CT:** minimal suprasternal extension; no tracheal compression.
- **Ultrasound (U3):** well-circumscribed, heterogeneously hypoechoic right lobe nodule, 52 × 36 × 30 mm; vascular, no microcalcification.

Discussion

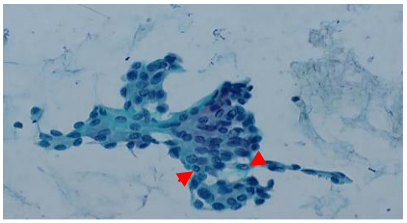
- Encapsulation, interface microfollicles and no well-formed papillae despite complete sampling kept NIFTP in the differential.
- Against it were nested and trabecular growth, abortive papillae, intranuclear inclusions and a positive BRAF V600E on IHC. BRAF V600E is classically a PTC marker, though there have been previous reports of NIFTP expressing BRAF V600E [5].
- IHC was also positive for CK19 which is seen in both NIFTP and PTC [6,7].
- Molecular testing was the tie breaker. The presence of BRAF V600E and absence of the expected RAS-like molecular profile of NIFTP led to PTC as the favoured diagnosis.
- Molecular testing also revealed a TERT promoter mutation.
- Traditionally, coexisting BRAF V600E and TERT promoter mutations are thought to have synergistic effect in PTC, increasing risk of recurrence and mortality compared to either mutation alone [8].
- However, the precise TERT variant may be of clinical significance, as emerging research indicates the rarer C250T variants may not have as aggressive an oncogenic effect compared to the more common C228T variant [9].

Looking Forward

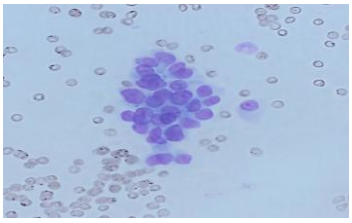
Ongoing research reveals potential future benefits of molecular testing in NIFTP and PTC management.

- A recent study raises the potential of molecular profiling of FNA being used to distinguish some PTCs from NIFTP, allowing optimisation of preoperative decision-making regarding management and follow up [10].
- Molecular testing may identify targets for future drug treatments. Dabrafe nib + trametinib has been trialled as a second line regime for BRAFV600E positive tumours that have been refractory to radioactive iodine treatment. [11]

Cytology

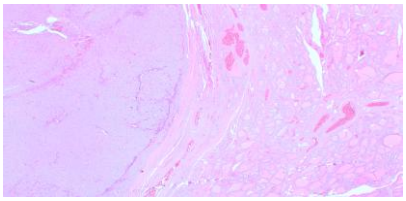


FNA (PAP): crowded sheet of follicular epithelial cells with enlarged, crowded and elongated nuclei, with intra nuclear inclusions (arrow)

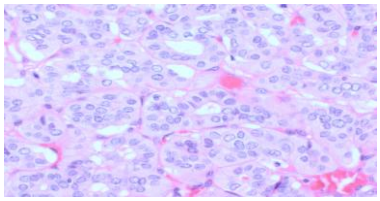


FNA (MGG): papillaroid fragment of follicular cells with intranuclear pseudoinclusions.

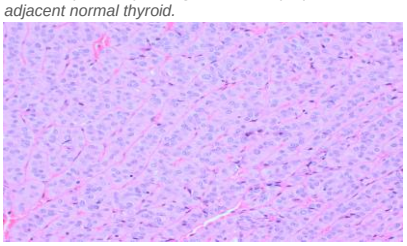
Histology



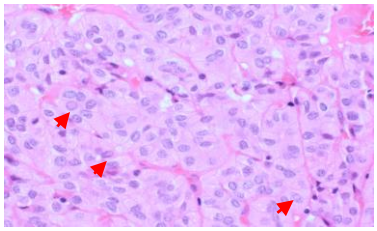
H&E:, X2 showing tumour - capsule interface showing fibrous capsule separating the tumour (left) from adjacent normal thyroid.



H&E, X40 tumour cells with a microfolliicular growth pattern.



H&E, X40 : tumour cells arranged in trabeculae, separated by thin fibrovascular septa, with PTC-type nuclear features.



H&E, X40 tumour cells with enlarged, overlapping nuclei and prominent intranuclear pseudoinclusions (arrows).

Molecular pathology (NGS panel, The Royal Marsden)

Gene	Variant
BRAF	c.1799T>A p.(Val600Glu)
TERT promoter	c.-146C>T (C250T)
KRAS, NRAS, HRAS, TP53, ALK, RET, ERBB2, MET	No oncogenic variant

DIAGNOSIS: encapsulated, well-differentiated papillary thyroid carcinoma with trabecular and microfollicular architecture

Conclusion

This is a case of an encapsulated, well differentiated papillary thyroid carcinoma with trabecular and microfollicular architecture, where molecular testing played a key role in distinguishing between a benign entity, NIFTP, and a malignant one, PTC. Molecular testing can enable personalised patient care through its role in diagnosis and prognostication with implications for management including identifying future drug targets.

References

1. Zhang J, Xu S. High aggressiveness of papillary thyroid cancer: from clinical evidence to regulatory cellular networks. *Cell Death Discov* 2024; **10**: 378
2. Agrawal N, Akbani R, Aksoy BA, *et al.* Integrated Genomic Characterization of Papillary Thyroid Carcinoma. *Cell* 2014; **159**: 676-690
3. Recommendations | Thyroid cancer: assessment and management | Guidance | NICE. https://www.nice.org.uk/guidance/ng230/chapter/Recommendations, [accessed 27 October 2026]
4. Nikiforov YE, Seethala RR, Tallini G, *et al.* Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. *JAMA Oncol* 2016; **2**: 1023
5. Lee SE, Hwang TS, Choi Y-L, *et al.* Molecular Profiling of Papillary Thyroid Carcinoma in Korea with a High Prevalence of *BRAF*^{V600E} Mutation. *Thyroid* 2017; **27**: 802-810
6. Khurana KK, Truong LD, LiVolsi VA, *et al.* Cytokeratin 19 Immunolocalization in Cell Block Preparation of Thyroid Aspirates: An Adjunct to Fine-Needle Aspiration Diagnosis of Papillary Thyroid Carcinoma. *Archives of Pathology & Laboratory Medicine* 2003; **127**: 579-583
7. Raphael SJ, McKeown-Eyssen G, Asa SL. High-molecular-weight cytokeratin and cytokeratin-19 in the diagnosis of thyroid tumors. *Mod Pathol* 1994; **7**: 295-300
8. Liu R, Xing M. TERT promoter mutations in thyroid cancer. *Endocr Relat Cancer* 2016; **23**: R143-155
9. Marczyk VR, Maia AL, Goemann IM. Distinct transcriptional and prognostic impacts of TERT promoter mutations C228T and C250T in papillary thyroid carcinoma. *Endocrine-Related Cancer* 2024; **31**: e240058
10. Brandler TC, Zhou F, Liu CZ, *et al.* Molecular Profiles of Noninvasive, Minimally Invasive, and Invasive Follicular Patterned Thyroid Neoplasms with Papillary Nuclear Features. *Thyroid* 2023; **33**: 715-723
11. Gao M, Park YJ, Lin C-C, *et al.* Efficacy and safety of dabrafenib plus trametinib in adults with differentiated thyroid cancer: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2026; **27**: 994-1003