Check for updates

CASE REPORT

REVISED Case Report: Multifocal non-invasive follicular thyroid neoplasm with papillary-like nuclear features presenting in a female child [version 2; peer review: 2 approved]

Asmaa Gaber Abdou , Hayam Aiad, Nancy Asaad

Department of Pathology, Menoufia University, Shebein Elkom, Menoufia, 32511, Egypt

V2 First published: 25 Jun 2020, 9:645
<https://doi.org/10.12688/f1000research.23687.1>
 Latest published: 21 Sep 2020, 9:645
<https://doi.org/10.12688/f1000research.23687.2>

Abstract

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced as a separate entity by the World Health Organization in 2017 with strict inclusion and exclusion criteria. Most NIFTP cases have been reported in adults and few cases have been diagnosed in children. Here, we present a classic case of NIFTP affecting a 10-year old female child. We also review previous reports of NIFTP in children regarding size, focality, nodal metastasis, recurrence, type of operation and follow-up data. The present report adds a new case of NIFTP in the paediatric age group characterized by multifocality, absence of nodal invasion and indolent course until last follow-up, recommending less aggressive management.

Keywords

NIFTP, children, multifocality

Open Peer Review

Approval Status

	1	2
version 2 (revision) 21 Sep 2020		 view
version 1 25 Jun 2020	 view	

1. **Hanan Alshenawy** , Tanta University, Tanta, Egypt
2. **Osama Sharaf Eldin** , Weston General Hospital, Weston-super-Mare, UK

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Asmaa Gaber Abdou (asmaa_elsaidy@yahoo.com)

Author roles: **Abdou AG:** Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Aiad H:** Conceptualization, Supervision; **Asaad N:** Supervision

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2020 Abdou AG *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Abdou AG, Aiad H and Asaad N. **Case Report: Multifocal non-invasive follicular thyroid neoplasm with papillary-like nuclear features presenting in a female child [version 2; peer review: 2 approved]** F1000Research 2020, 9:645
<https://doi.org/10.12688/f1000research.23687.2>

First published: 25 Jun 2020, 9:645 <https://doi.org/10.12688/f1000research.23687.1>

REVISED Amendments from Version 1

More details have been added to the discussion section.

Any further responses from the reviewers can be found at the end of the article

Introduction

Generally, the diagnosis of papillary thyroid carcinoma (PTC) has increased over the past several decades¹, partly due to increased recognition of the follicular variant of PTC². The subjectivity in diagnosis of this variant and the indolent behaviour of encapsulated or non-invasive forms, led to revision and follow-up of a large number of these cases by international multidisciplinary collaborative group^{3,4}. Consequently, the encapsulated variant of PTC was reclassified as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), which had strict inclusion and exclusion criteria for this diagnosis. The term NIFTP was then introduced as a separate entity by the World Health Organization in 2017, with a category of follicular tumour of uncertain malignant potential and well-differentiated tumour of uncertain malignant potential⁵. The majority of NIFTP reports have been in adults. Here, we present a classic case of NIFTP affecting a 10-year old female child.

Case report

A female patient of 10 years presented to our department with an enlarged thyroid that had been observed by her mother. No previous relevant family history was recorded.

Ultrasound revealed two suspicious nodules on the right side of the thyroid lobe. No pathological lymph node enlargement was reported. Ultrasound guided fine needle aspiration cytology was performed and the results showed sheets of follicular epithelial cells, some were elongated with occasional nuclear grooves and inclusions (Figure 1A). This was diagnosed as atypical thyroid lesion indefinite for malignancy (THY3a).

The patient was submitted for total thyroidectomy within one month from her first presentation. On resection, the right thyroid lobe measured 5.5 × 3.5 × 3 cm with two well-defined, firm, grayish white nodules. One nodule measured 2 × 1.5 cm and the other measured 1.5 × 1.5 cm (Figure 1B). The left lobe and isthmus measured 4.5 × 3 cm and 1 × 0.5 cm, respectively.

Histological examination of the two nodules resected from the right thyroid lobe revealed well-circumscribed capsulated nodules formed of microfollicles, lined by follicular epithelial cells with wide-spread nuclear features of papillary thyroid carcinoma (Figure 1C). There was no evidence of capsular or vascular invasion, true papillae, trabeculae or solid arrangement. The patient did not receive any specific medications before surgery and she was followed up for 12 months with no evidence of recurrence or nodal involvement.

Discussion

Most NIFTP cases have been previously reported in adults and data concerning this diagnosis in children is scarce; only

21 cases in children have been reported in the English literature within the last two years (Table 1)^{6–10}. Preoperative diagnosis of our case was based on ultrasound data and the cytology was not obviously malignant. The cytologic smears of NIFTP were usually hypercellular showing follicular epithelial cells arranged in microfollicles without papillae formation and they showed subtle features of papillary thyroid carcinoma but with infrequent or absent nuclear inclusions. NIFTP cytology was commonly interpreted as follicular lesion of undetermined significance in 30% (categories III and IV according to Bethesda system), follicular neoplasm in 21%, suspicious for malignancy in 24%, malignant in 8%, benign in 10% and non-diagnostic in 3%^{11,12}. Although the above findings would suggest lobectomy, our patient was submitted for total thyroidectomy and as has been done in previously reported cases^{6,7,9,10}.

On a molecular level, NIFTP shares follicular neoplasm in RAS mutations but it lacks *BRAF*^{V600E} mutations, which is a common event in papillary thyroid carcinoma¹³. Immunohistochemistry for *BRAF*^{V600E} mutations is available on paraffin blocks. Nuclear pseudoinclusions are important diagnostic criteria for PTC, which could be highlighted by CK19 immunostaining in comparison to routine hematoxylin and eosin¹⁴. The latter authors demonstrated absence of CK19 positive nuclear pseudoinclusions in the investigated 7 cases of NIFTP.

The current report demonstrated a classic case of NIFTP affecting a young female child, agreeing with previous reports that there are more cases in women than men (Table 1). Although

Figure 1. Right thyroid lobe results from patient. (A) Cytologic features of fine needle aspiration cytology showing cohesive sheet of follicular epithelial cells, including some which were rounded and others that were elongated with occasional grooved nuclei (hematoxylin and eosin, mag. ×600). **(B)** Gross picture of affected right lobe after total thyroidectomy showing two well circumscribed whitish nodules. **(C)** Histopathological examination of nodule of resected thyroid revealing a capsulated nodule formed of microfollicles lined by follicular epithelial cells, which had enlarged pale crowded nuclei together with nuclear grooves and inclusions (nuclear features of papillary thyroid carcinoma)(hematoxylin and eosin, mag. ×400).

Table 1. Characteristics of reported non-invasive follicular thyroid neoplasm with papillary-like nuclear features in children.

	Age (years)	Gender F:M	Size (cm)	Focality	Recurrence	Metastasis	Operation	Follow up (months)
Wang <i>et al.</i> , 2019 (3 cases) ⁶	16–17	2:1	0.4–3.1	Single	No	No	Total thyroidectomy	15–138
Rosario and Mourão, 2018 (4 cases) ⁷	9–15	3:1	1.7–2.4	Single	No	No	Total thyroidectomy	24–108
Rossi <i>et al.</i> , 2018 (2 cases) ⁸	<19	1:1	<2 > 2	Single	No	No	NA	84
Mariani <i>et al.</i> , 2018 (10 cases) ⁹	14.4	3.5:1	2.1	7 cases single 3 cases multifocal	No	2 cases with lymph node metastases	Total thyroidectomy	NA
Samuels <i>et al.</i> , 2018 (2 cases) ¹⁰	14	2:1	1.1–4.5	NA	No	No	Total thyroidectomy	NA
The current case	10	Female	1.5–2	Multifocal	No	No	Total thyroidectomy	12

F:M, female to male ratio, NA: not available

not common, multifocality has been reported previously for NIFTP in adults¹⁵ and in children⁹. The size of NIFTP lesion is usually small, rarely exceeding 2 cm in diameter (Table 1).

More aggressive therapy is recommended for PTC in childhood and adolescence¹⁶ but the indolent behaviour reported for NIFTP necessitates less aggressive management in children, as well as adults. Therefore, completion lobectomy is not recommended for postoperative cases diagnosed as NIFTP⁸. NIFTP in children has a similar outcome as cases reported in adults, suggesting that paediatric NIFTP behaves indolently, as evidenced by the absence of local recurrence and nodal metastasis⁶.

The present report adds a new case of NIFTP in the paediatric age group characterized by multifocality, absence of nodal invasion and indolent course - until last follow-up, recommending less aggressive management of this disease.

Consent

Written informed consent was obtained from the patient's father for the publication of this case report and any associated images.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

References

- Davies L, Welch HG: **Increasing incidence of thyroid cancer in the United States, 1973–2002.** *JAMA*. 2006; **295**(18): 2164–2167.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jung CK, Little MP, Lubin JH, *et al.*: **The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of *BRAF* mutations and a sharp increase in *RAS* mutations.** *J Clin Endocrinol Metab*. 2014; **99**(2): E276–E285.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- 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**(8): 1023–1029.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Thompson LD: **Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment.** *Mod Pathol*. 2016; **29**(7): 698–707.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lloyd RV, Osamura RY, Klöppel J, *et al.*: **WHO Classification of Tumours of Endocrine Organs.** (4th edition), IARC: Lyon, France. 2017.
[Reference Source](#)
- Wang H, Correa H, Sanders M, *et al.*: **Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features in Children: An Institutional Experience and Literature Review.** *Pediatr Dev Pathol*. 2020; **23**(2): 121–126.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rosario PW, Mourão GF: **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in children and adolescents.** *Endocrine*. 2018; **61**(3): 542–544.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rossi ED, Mehrotra S, Kilic AI, *et al.*: **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in the pediatric age group.** *Cancer Cytopathol*. 2018; **126**(1): 27–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mariani RA, Kadakia R, Arva NC: **Noninvasive encapsulated follicular variant of papillary thyroid carcinoma: Should it also be reclassified in children?** *Pediatr Blood Cancer*. 2018; **65**(6): e26966.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Samuels SL, Surrey LF, Hawkes CP, *et al.*: **Characteristics of Follicular Variant Papillary Thyroid Carcinoma in a Pediatric Cohort.** *J Clin Endocrinol Metab*. 2018; **103**(4): 1639–1648.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rosario PW, Mourão GF, Nunes MB, *et al.*: **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features.** *Endocr Relat Cancer*. 2016;

- 23(12): 893–897.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Bongiovanni M, Giovanella L, Romanelli F, *et al.*: **Cytological Diagnoses Associated with Noninvasive Follicular Thyroid Neoplasms with Papillary-Like Nuclear Features According to the Bethesda System for Reporting Thyroid Cytopathology: A Systematic Review and Meta-Analysis.** *Thyroid*. 2019; **29**(2): 222–228.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Howitt BE, Paulson VA, Barletta JA: **Absence of BRAF V600E in non-infiltrative, non-invasive follicular variant of papillary thyroid carcinoma.** *Histopathology*. 2015; **67**(4): 579–582.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Domagala P, Domagala W: **Nuclear CK19-immunopositive pseudoinclusions as a new additional objective diagnostic feature of papillary thyroid carcinoma.** *Pol J Pathol*. 2020; **71**(1): 1–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Fonseca D, Bhuyan S, Murthy SS, *et al.*: **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: A distinct clinicopathologic entity.** *Indian J Pathol Microbiol*. 2018; **61**(3): 380–382.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Francis GL, Waguespack SG, Bauer AJ, *et al.*: **Management Guidelines for Children with Thyroid nodules and Differentiated Thyroid Cancer.** *Thyroid*. 2015; **25**(7): 716–59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:

Version 2

Reviewer Report 28 October 2020

<https://doi.org/10.5256/f1000research.29612.r69816>

© 2020 Eldin O. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Osama Sharaf Eldin

Weston General Hospital, Weston-super-Mare, UK

The case is well written and with full explanation of the diagnostic category. The introduction included the accurate classification of the entity and why the nomenclature changed. The figures and tables are well presented. The references are up to date.

No further comments and I agree for this case report to be indexed without changes.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular Pathology, Digital Pathology and experimental pathology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 29 Oct 2020

Asmaa Abdou, Menoufia University, Shebein Elkom, Egypt

Dear Sir

Thanks for your review and judgment, according to your comments, no changes are required

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 08 September 2020

<https://doi.org/10.5256/f1000research.26135.r70314>

© 2020 Alshenawy H. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Hanan Alshenawy

Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

This is a case report about a case of NIFTP in thyroid.

- The case is well clinically presented with full clinical data.
- The procedure as FNAC is also presented well with clear figure.
- Histopathology is shortly presented with clear good figure.
- The discussion should be in more details.
- Is there any role for immunohistochemistry?

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: histopathology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research