



Case series

What you see might not be what you get: Analysis of 15 prospective cases of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

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ARTICLE INFO

Keywords:

NIFTP

Papillary thyroid carcinoma

Noninvasive

Follicular thyroid neoplasm

Papillary-like nuclear features

Nodule

ABSTRACT

Introduction: Noninvasive follicular thyroid neoplasm with papillary-like nuclear (NIFTP) is a new entity. No previous study reported prospective cases, outlining using many quantitative and qualitative variables.

Methods: Retrospective analysis of all (15) prospective NIFTP cases diagnosed between 2017 and 2021 at our institution. Statistical quantitative analysis outlined demographic, history, ultrasound, histopathology and treatment characteristics. Qualitative analysis examined the cases, with details provided on three cases to highlight the different possible presentations and configurations.

Results: Mean age was 41.5 ± 9.91 years, 73.3% were females, and mean BMI was 29.49 ± 5.74 kg/m². About 87% patients were symptomatic; 86.6% had neck swelling. Ultrasound (US) showed multiple nodules in 71.4% of cases. Fine-needle aspiration cytology (FNAC) showed that follicular lesion of undetermined significance (42.8%) was most common, followed by benign nodule (21.3%). Using the Bethesda System for Reporting Thyroid Cytopathology, 7 cases were category III, 3 category IV, 3 category II, and 1 category I. 60% of patients underwent total thyroidectomy. All cases were diagnosed postoperatively, 2 patients had additional papillary microcarcinoma. In 3 cases, the NIFTP site in the histopathology of resected specimen was different than the US-recommended site of the FNAC.

Conclusion: We found discrepancies in the site and diagnosis of the preoperative US recommendation for the FNAC vs the postoperative histopathology of the specimen. These suggest that NIFTP might be incidentally and postoperatively diagnosed, irrespective of US or FNAC findings, hence its 'true' incidence might remain underestimated. As NIFTP cases higher BMI, Future research could predict preoperative diagnosis of NIFTP and explore associations with BMI.

1. Introduction

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a histological variant introduced in 2016 and recently recognized by The World Health Organization Classification of Tumors of Endocrine Organs [1,2]. The follicular variant of papillary thyroid carcinoma (PTC) comprises 9–22% of all PTC and is categorized into encapsulated or infiltrative types, where the term NIFTP replaced

the non-invasive encapsulated follicular variant, characterized by indolent course and very low malignant potential [3,4].

NIFTP cases present similar to most thyroid nodules that are usually detected by physical examination or ultrasound (US) [5]. However, diagnostic US does not allow identification of NIFTP [6]. All NIFTP are diagnosed post-surgical after fulfillment of a set of criteria on the resected specimen such as full encapsulation or complete circumscription of the tumor, nuclear features of PTC, follicular pattern of growth

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<https://doi.org/10.1016/j.ijscr.2021.106751>

Received 15 November 2021; Received in revised form 31 December 2021; Accepted 31 December 2021

Available online 5 January 2022

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with no psammoma bodies, no capsular or vascular invasion, and no evidence of necrosis [7].

We report a retrospective analysis of 15 prospective cases from a single center. All the cases were diagnosed over the last five years (2017–2021) after the introduction of the term NIFTP. We present a quantitative breakdown in terms of the demographic, history, ultrasound, histopathology and treatment characteristics of the cases. In addition, we also present a qualitative analysis, where we highlight the characteristics of each individual case, and after examining the 15 cases, exhibit in detail one fairly traditional case and two atypical cases, in order to draw attention to the different possible presentations and configurations of NIFTP. This report is in line with the updated consensus-based case series (PROCESS) guidelines [8].

2. Methods

The current series retrospectively analyzed 15 consecutive prospective cases diagnosed during the last five years at our institution (Hamad General Hospital, largest tertiary facility in Doha, Qatar). The study was approved by the Medical Research Center, Hamad Medical Corporation IRB (MRC# 04-21-906).

Seven patients signed informed consents; 3 patients provided verbal consent over the telephone witnessed by a second co-author; 3 cases could not be reached despite the exhaustive attempts made to contact them or their families, and one case had travelled outside of the country. Data was retrieved from the electronic patient database of our institution; and the paper was sufficiently anonymized not to cause harm to any of the patients or their families.

All the cases diagnosed as NIFTP during the study period were included. All patients were previously healthy except one who had epilepsy and migraine, and 3 had hypertension and were on medications. Surgery was indicated for all the patients and undertaken by senior consultant surgeons with no complications and unremarkable post-operative course. All cases were discussed at the Thyroid multidisciplinary team (MDT) meetings regarding diagnosis, management plan, and follow up. Preoperative data retrieved included demographic, history, thyrotropin (TSH) and vitamin D levels, treatment, ultrasound features, and histopathology and cytology characteristics of the lesions; postoperative data included radioactive iodine treatment, completion surgery and post-operative thyroglobulin levels.

Statistical quantitative analysis was conducted for demographic, history, US, histopathology and treatment characteristics and results were presented as terms of mean \pm standard deviation for continuous variables and frequency/percentage for categorical variables. Qualitative analysis examined all the cases, with detailed descriptions of one fairly traditional case and two atypical cases.

3. Results

3.1. Demographic, history and treatment characteristics

Demographically, the sample's mean age was 41.5 ± 9.91 years, comprised 73.3% females, and all were overweight (mean BMI 29.49 ± 5.74 kg/m²). About one third of the cases were Qatari nationals while the rest of patients were from Egypt (4, 26.6%), Filipino (3, 20%), Tunisian (1, 6.6%), Pakistani (1, 6.6%), Indian (1, 6.6%). In term of history and treatment, Table 1 shows that a minority (13.3%) of cases were discovered incidentally, most (86.6%) patients were symptomatic, and the most common symptom was neck swelling (86.6%). Mean duration of symptoms was 22.1 ± 17.5 months, and none of the patients had history of neck irradiation or family history of thyroid cancer. Most (93.3%) patients were euthyroid (mean TSH 1.7 ± 1.09 mIU/l) and vitamin D insufficient (mean vitamin D 25.1 ± 9.38 ng/ml). As for treatment, 9 patients (60%) had lobectomy, 6 (40%) had total thyroidectomy, 3 cases (19.9%) received post-operative radioactive iodine (RAI) ablation and another 2 cases (13.3%) had completion surgery. The

Table 1

History and treatment characteristics of the sample.

Characteristic	Value
BMI (kg/m ²) M \pm SD	29.49 \pm 5.74
Comorbidities	
No	11 (73.3)
Yes ^a	4 (26.6)
Incidental presentation	
No	13 (86.6)
Yes ^b	2 (13.3)
History	
Family thyroid cancer	0 (0)
Neck irradiation	0 (0)
Swelling	
No	2 (13.3)
Yes	13 (86.6)
Compression symptoms	
No	9 (60)
Yes	6 (40)
Duration of symptoms (months) ^c	
M \pm SD with 1 outlier	44.1 \pm 70.79
M \pm SD without outlier	22.1 \pm 17.5
Thyroid state	
Euthyroid	14 (93.3)
Hypothyroid	1 (6.6)
TSH (mIU/L) M \pm SD	1.7 \pm 1.09
Vitamin D (ng/ml) M \pm SD	25.1 \pm 9.38
Treatment n (%)	
Type of surgery	
Lobectomy	9 (60)
Total thyroidectomy	6 (40)
Date of surgery	
2017	1 (6.6)
2018	2 (13.3)
2019	3 (20)
2020	6 (40)
2021	3 (20)
Post-operative RAI	
No	12 (80)
Low dose	2 (13.3)
Unknown dose ^d	1 (6.6)
Completion surgery	
No	13 (86.6)
Yes	2 (13.3)
Thyroglobulin (ng/ml) M \pm SD	
Post-operative	4.56 \pm 4.95
Last recorded	2.8 \pm 3.14

All cells represent n (%) except where indicated.

^a 1 patient had epilepsy and migraine, 3 had hypertension.

^b 1 patient discovered during routine women-well screening in Thailand, another discovered during routine medical workup at the Medical Commission in Qatar.

^c There was one outlier value (240 months), so M \pm SD are presented with and without the outlier.

^d Radioactive iodine dose unknown as the patient sought treatment overseas (Thailand) and dose was delivered there.

Valid percentages reported, numbers might not always add to N = 15 due to missing values; RAI: radioactive iodine.

mean post-operative thyroglobulin was 4.56 ± 4.95 ng/ml; after follow up, as some cases had completion treatment, mean thyroglobulin was reduced to 2.8 ± 3.14 ng/ml.

3.2. Ultrasound characteristics

US of the thyroid showed that 10 cases (76%) had multiple nodules (Table 2). The mean size of nodules in the right and left lobes and isthmus was 3.44 ± 1.82 , 3.44 ± 1.88 and 2.11 ± 0.24 cm respectively; and the average size of the largest nodule was 4.11 ± 1.39 cm. Nodules were more common in the left (71.4%) than in the right lobe (28.5%). Suspected abnormality/ies were observed in the left (50%) and right lobes (35.7%), or were bilateral (14.2%). Regarding echogenic, composition, shape and margin abnormalities, the most common

Table 2
Thyroid ultrasound characteristics of the sample.

Characteristic	Value
Number of nodules	
Single	4 (28.5)
Multiple	10 (71.4)
Size of nodule (cm) M ± SD	
Right lobe	3.44 ± 1.82
Left lobe	3.44 ± 1.88
Isthmus	2.11 ± 0.24
Largest nodule	
Size (cm) M ± SD	4.11 ± 1.39
Site	
Right	4 (28.5)
Left	10 (71.4)
Suspected abnormality/ies	
Site	
Right	5 (35.7)
Left	7 (50)
Bilateral	2 (14.2)
Type	
Cystic	1 (7.6)
Complex	8 (61.5)
Hypoechoic	2 (15.3)
Isoechoic	2 (15.3)
Vascularity	
No	6 (40)
Yes	9 (60)
Type	
Intranodular	4 (40)
Perinodular	4 (40)
Both	2 (20)
Calcification	
No	13 (86.6)
Micro	1 (6.6)
Macro	1 (6.6)
Lymphadenopathy	
Present	
No	4 (26.6)
Yes	11 (73.3)
Malignant features	
No	15 (100)
Yes	0 (0)
Site	
Bilateral non-specific LN	9 (90)
Right submandibular	1 (10)

All cells represent n (%) except where indicated; LN: lymph node; valid percentages are presented, numbers might not always add to N = 15 due to missing values.

suspicious finding was a complex nodule (61.5% of cases), and no calcification was observed in the majority (86.6%) of cases. A total of 9 cases (64.2%) displayed increased vascularity of the nodule, and 73.3% of cases had sonographic evidence of lymphadenopathy, all of which were non-specific with no malignant features.

3.3. Histopathology and cytology characteristics of the lesions

Table 3 depicts that preoperative FNAC (fine needle aspiration and cytology) was undertaken for 14 of the 15 cases. The most common finding was follicular lesion of undetermined significance (FLUS) (42.8%) followed by benign nodule (colloid nodule or colloid and Hurthle cell changes) (21.3%). Using the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), 7 cases were category III (50%), 3 were category IV (21.4%), 3 category II (21.4%), and 1 category I (7.1%). The decision for surgery was premised after discussing the findings of the FNAC and US at the Thyroid MDT meeting (except case 13 where surgery was done because patient was symptomatic). Postoperatively, the histopathology of all the surgical excised specimens showed features of NIFTP. Two specimens (13.3%) had both NIFTP and papillary microcarcinoma (PMC). The site of the pathology was equal in the right lobe (46.6%) and left lobe (46.6%), and 1 case had two pathologies (NIFTP +

Table 3
Histopathology and cytology characteristics of the lesions.

Characteristic	Value
Preoperative	
US guide thyroid FNAC	
FLUS	6 (42.8)
Follicular neoplasm	3 (21.4)
Colloid nodule	2 (14.2)
Colloid and Hurthle cell changes	1 (7.1)
Atypical	1 (7.1)
Inadequate	1 (7.1)
Bethesda category	
I	1 (7.1)
II	3 (21.4)
III	7 (50)
IV	3 (21.4)
V	0 (0)
VI	0 (0)
Histopathology	
NIFTP	13 (86.6)
NIFTP+PMC	2 (13.3)
Site of pathology	
Right	7 (46.6)
Left	7 (46.6)
Bilateral	1 (6.6)
Number of foci	
Unifocal	13 (86.6)
Multifocal	2 (13.3)
Size of foci (cm) ^a M ± SD	2.1 ± 1.75

All cells represent n (%) except where indicated; US: ultrasound; FNAC: fine needle aspiration and cytology; FLUS: follicular lesion of undetermined significance.

^a Mean size of foci = sum of all unifocal lesions and the largest foci in the multifocal lesions divided by the number of lesions; valid percentages are presented; numbers might not always add to N = 15 due to missing values.

PMC) in both lobes. As for the foci, 86.6% of cases were unifocal and 13.3% were multifocal, with the mean size of the foci being 2.1 ± 1.75 cm. Fig. 1 depicts the histopathology characteristics.

4. Case presentations

4.1. Case 1

A 41-year-old Egyptian male presented to our Thyroid Surgery clinic (Hamad General Hospital, largest tertiary facility in Doha, Qatar) in December 2017 with non-painful swelling in the left side of the neck, no change in voice, odynophagia, or other complaints. Past medical, surgical, social, environmental, family, neck radiotherapy exposure and employment history were unremarkable. On examination, vital signs were normal, BMI was 28.73 kg/m² and there was a mobile left sided neck swelling that moved with swallowing. Thyroid function tests were within normal. Thyroid US showed a well-defined solid nodule (5.18 × 2.78 cm) at the lower part of left thyroid lobe (Fig. 2A). There was mild internal vascularity, no calcifications or cystic changes (Fig. 2B), and there was bilateral cervical reactive lymphadenopathy. US-guided FNAC of the left thyroid nodule showed FLUS. The surgical team decided to undertake elective left hemithyroidectomy. The post-operative course was uneventful and the patient was discharged after 1 day. Post-operative histopathology showed left thyroid NIFTP. The findings were discussed at the Thyroid MDT meeting and the decision was follow up at the Endocrinology Thyroid Cancer clinic with thyroid US and thyroglobulin scheduled in 6 months.

4.2. Case 2, unusual: pre-operative US showed left thyroid lobe with abnormal nodule; post-operative histopathology confirmed PMC with multifocal NIFTP in both thyroid lobes

A 33-year-old Egyptian female presented to the Thyroid Surgery clinic at our institution (Hamad General Hospital in Doha, Qatar) in

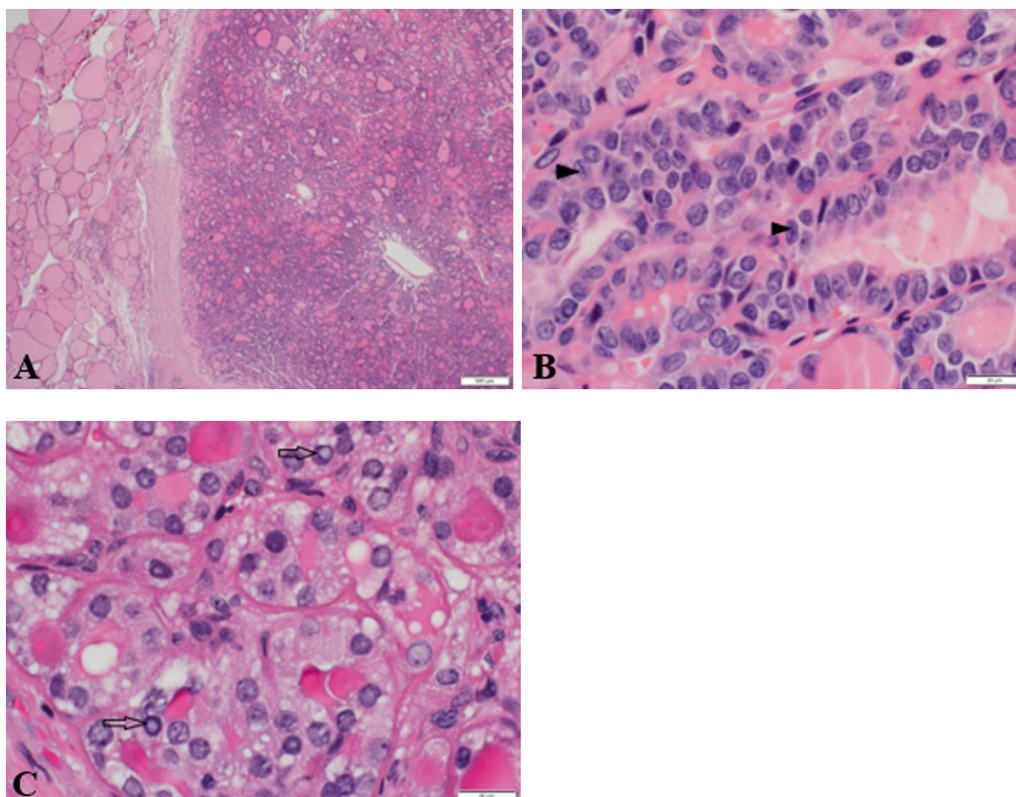


Fig. 1. A) Low power view showing a well circumscribed NIFTP in the right, with normal thyroid parenchyma on the left (H and E \times 2); B) the NIFTP shows features similar to papillary thyroid carcinoma, including irregular nuclear outlines, nuclear irregularities and prominent grooves (black arrowhead) (H and E \times 60); C) occasional foci of pseudoinclusions are also noted (arrows) (H and E \times 60).

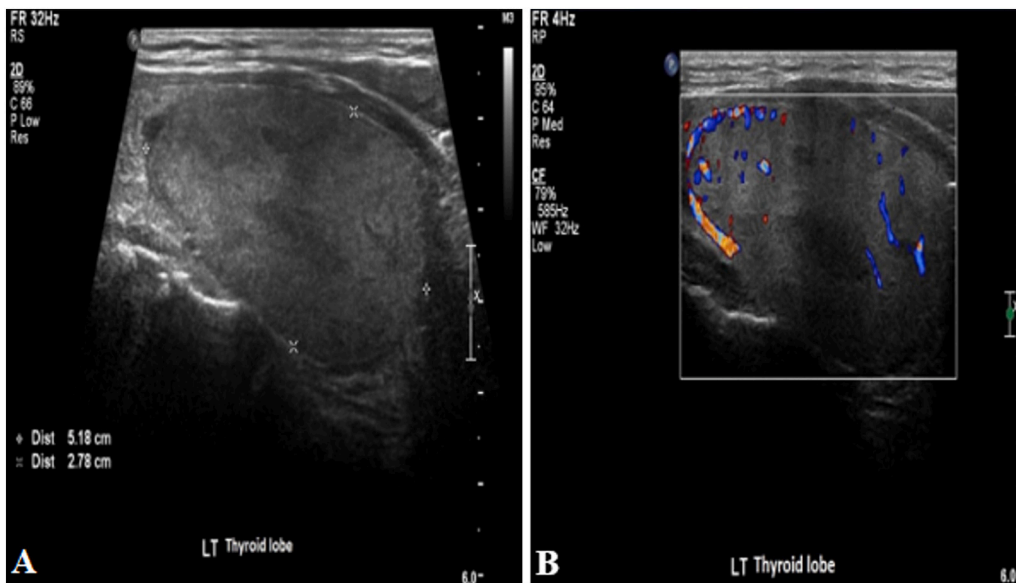


Fig. 2. Ultrasound of left thyroid lobe showing: A) well-defined solid nodule (5.18 \times 2.78 cm) at the lower part; and, B) well-defined solid nodule with mild internal vascularity, but no calcifications or cystic changes.

October 2019 with a left-sided neck swelling of 4 years duration associated with right neck pain. There was no change in voice, no odynophagia, and no other complaints. Past medical, surgical, social, environmental, family, neck radiotherapy exposure and employment history were unremarkable. Vital signs were normal, BMI was 26.11 kg/m² and neck examination revealed left sided, firm, mobile and non-tender anterior neck swelling, but no palpable lymph nodes. Thyroid

function tests were within normal and vitamin D level was insufficient (22 ng/ml). Thyroid US showed complex nodule (4.2 \times 1.8 \times 2.2 cm) occupying almost the entire left lobe, containing a cyst with thick irregular wall and clear content (Fig. 3A), with no obvious internal vascularity but with peripheral vascularity (Fig. 3B). Bilateral US-guided FNAC showed bilateral FLUS. At the Thyroid MDT meeting, the decision was to undertake total thyroidectomy. She was admitted for elective

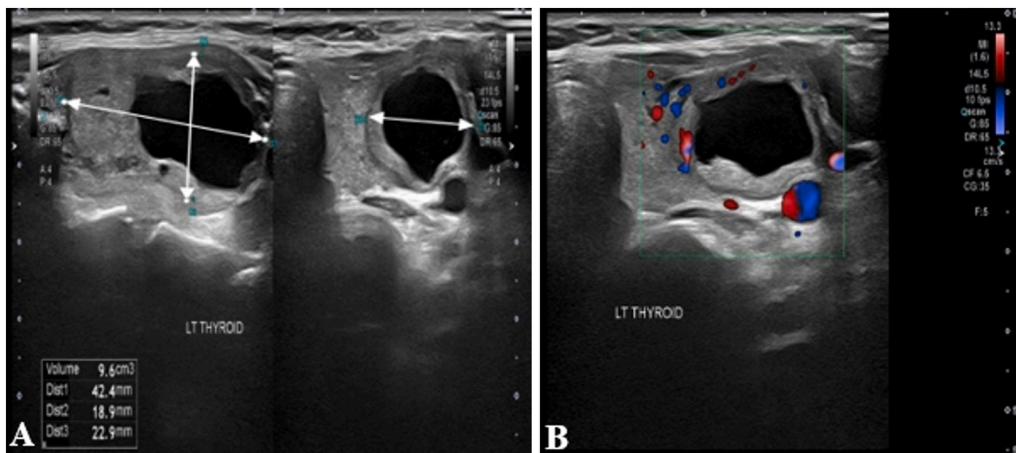


Fig. 3. Ultrasound of left thyroid lobe showing: A) complex nodule (4.2 × 1.8 × 2.2 cm) occupying almost the entire lobe, containing cyst with thick irregular wall and clear content; and, B) complex nodule with peripheral vascularity, and no obvious internal vascularity.

total thyroidectomy. The post-operative course was uneventful and the patient was discharged after 1 day. Post-operative histopathology showed bilateral PMC with multifocal NIFTP located in the right and left thyroid lobes (0.8 cm and 0.3 cm respectively). The margins and lymphatic invasion were negative. There were additional pathologic findings of lymphocytic thyroiditis and multinodular hyperplasia. The pathology was discussed again at the thyroid MDT meeting and the decision was for low dose radioactive iodine (RAI) treatment and follow up at the Endocrinology Thyroid Cancer clinic with thyroid US and thyroglobulin scheduled in 6 months. The patient was seen after 1 month at Thyroid Surgery clinic and she had no active issues.

4.3. Case 3, unusual: multinodular goiter diagnosed by FNAC; second FNAC at 1 year diagnosed follicular lesion of Hurthle cell type recommending total thyroidectomy; post-operative histopathology confirmed NIFTP

A 52-year-old Qatari female referred to the Thyroid Surgery clinic at our institution (Hamad General Hospital in Doha, Qatar) in April 2019 for surgical treatment as a case of symptomatic multinodular goiter (MNG) diagnosed in 2018 (FNAC at that time showed colloid nodule). She complained of intermittent compression symptoms, difficulty on swallowing, difficulty of breathing and neck swelling. There was no change in voice, no odynophagia, and no other complaints. Past surgical

history was significant for liposuction, but past medical, social, environmental, family, neck radiotherapy exposure and employment history were unremarkable. Vital signs were normal, BMI was 30.36 kg/m² and neck examination showed mobile and non-tender left palpable neck swelling. Thyroid function tests were within normal. Thyroid US showed well-defined solid hypoechoic nodule (1.66 × 0.92 cm) in the mid part of the right lobe (Fig. 4A), with internal vascularity and a well-defined complex nodule (2.53 × 1.06 cm) at the lower part with mild internal vascularity and calcifications (Fig. 4B). On the lower part of the left side, there was a well-defined complex hypoechoic nodule (5.28 × 2.81 cm) with internal vascularity and calcifications; and another well-defined complex hypoechoic nodule (2.91 × 2.24 cm) at the upper part with internal vascularity (Fig. 5A and B). There was bilateral cervical nonspecific lymphadenopathy. US-guided FNAC of the thyroid nodules showed follicular lesion of Hurthle cell type from the right thyroid nodule, and cystic colloid from the left thyroid nodule. The patient was discussed at the Thyroid MDT and total thyroidectomy was decided. She was admitted for elective total thyroidectomy. Post-operative course was uneventful and the patient was discharged after 2 days. Post-operative histopathology showed left thyroid lobe NIFTP (4 mm) arising in a hyperplastic nodule. The pathology was discussed again at the MDT meeting and the decision was for periodic follow up at the Endocrinology Thyroid Cancer clinic with thyroid US and thyroglobulin. The patient was seen after 2 weeks at the Thyroid Surgery clinic, the

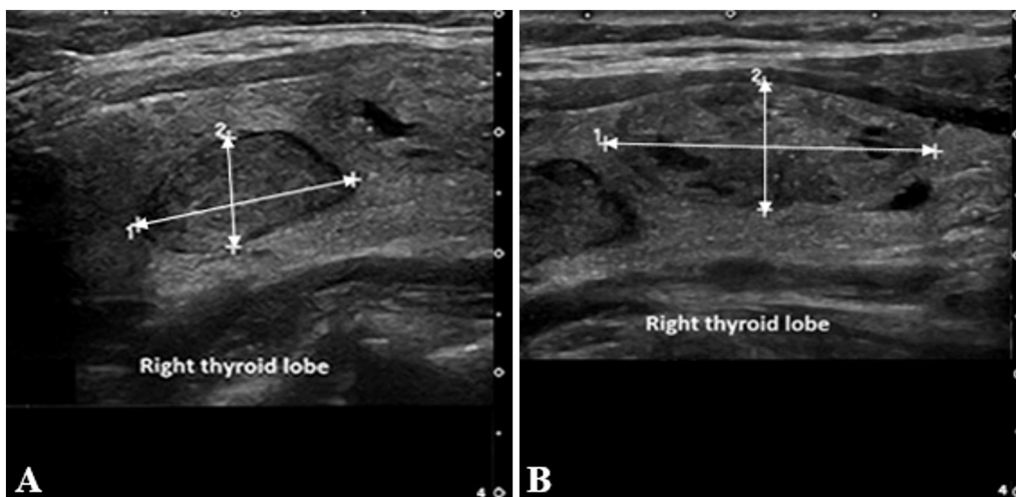


Fig. 4. Ultrasound of right thyroid lobe with: A) well-defined solid hypoechoic nodule at the mid part (1.66 × 0.92 cm), with no calcifications or cystic changes; and B) well-defined complex nodule at the lower part (2.53 × 1.06 cm), with calcifications.

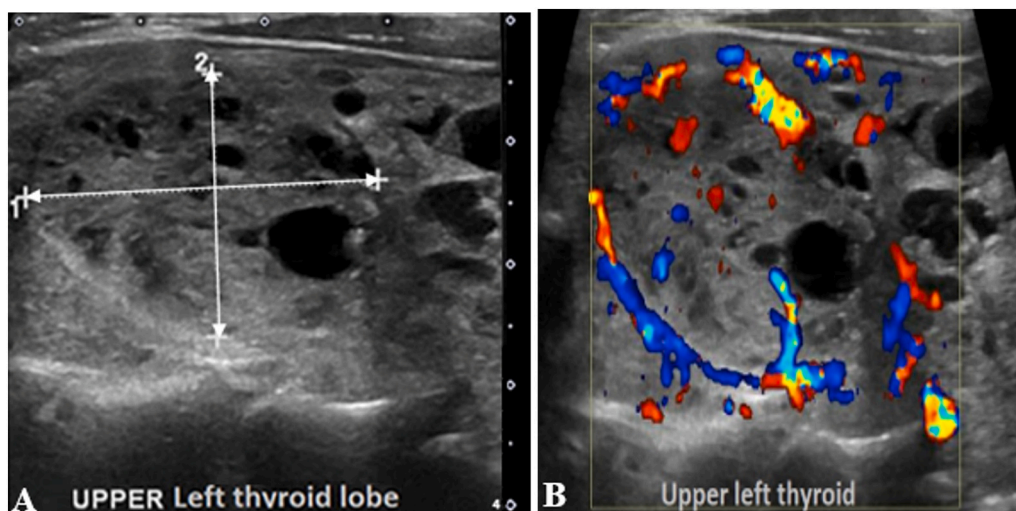


Fig. 5. Ultrasound of left thyroid lobe with: A) well-defined complex hypoechoic nodule at upper part (2.91 × 2.24 cm); and B) well-defined complex hypoechoic nodule with internal vascularity.

wound was clean and she had no active issues.

5. Discussion

The diagnosis of thyroid cancer has markedly increased with the advance of radiological screening, FNAC, and molecular analysis [9,10]. For this reason, the newer term NIFTP replaced the old term ‘non-invasive encapsulated follicular variant of papillary thyroid carcinoma’ to avoid overdiagnosis and overtreatment [11]. Despite this, the diagnostic criteria of NIFTP were revised in 2018, as several cases reported micrometastasis to the regional lymph nodes [12]. Thus, patients diagnosed with NIFTP still need to be followed up by annual thyroglobulin (TG) and occasionally thyroid US [13].

The current report presents a quantitative and qualitative retrospective analysis of 15 prospective cases from a single tertiary care centre. To our knowledge, this report could be the first to: 1) report prospective NIFTP cases; 2) present a wide range of quantitative data in terms of demographics, presentation, investigations (US thyroid, FNAC), management and postoperative histopathology; and, 3) elaborate qualitative (case details) data, highlighting unusual cases within the sample. A study in Turkey reported 84 NIFTP cases, however this study was retrospective, mainly quantitative with narrower focus (only treatment, pathological features, follow up), and provided no details on individual unusual cases within the 84 patients [14]. Likewise, a recent comprehensive literature search and meta-analysis that included 50 studies with 100,780 PTCs and 3990 NIFTPs from 92 institutions worldwide found that all the studies published were retrospective [15].

In term of demographics, Table 4 and the 3 represented cases (case 1 was an Egyptian male, case 2 was Egyptian female, and case 3 was Qatari female, diagnosed at age of 41, 33, and 52 respectively) shows that our patients’ mean age was 41.5 ± 9.91 years, and the condition was more common in females. This is consistent with other studies where mean age was 49.0 ± 12.9 and 49 ± 14.1 years respectively [14,16]. As for ethnicity, 60% of our cases were among Qatari and Egyptian patients, and less were among patients of Asian origin (e.g., Filipino, Pakistani, Indian) (Table 4). This concurs with a recent meta-analysis where NIFTP was significantly lower in Asia compared with North America and Europe [15]. Regarding BMI, we observed that $\approx 92\%$ of our patients were either overweight or obese (BMI range 29.49 ± 5.74 kg/m²) with only one exception (Cases 8 and 15, Table 4). The current study sheds important light on the potential incidence of NIFTP in the MENA (Middle East and North Africa) region, as only 1 study has been published from this region [14]. In addition, no previous studies seem to

have explored the association of BMI with NIFTP. Future research would benefit to assess whether high BMI could be potential risk factor for NIFTP.

As for presentation, 86.6% of our cases were symptomatic (Table 4), in agreement with others where 77.4% were symptomatic [16]. Likewise, 93.3% of our sample were euthyroid (Table 4), concurring with others where 92.8% of cases were euthyroid [17].

In connection with imaging, US was undertaken to detect any radiological abnormality and guide the FNA to the site of the suspected nodule. US of our sample showed that the average size of the largest nodule was 4.11 ± 1.39 cm and it was more on the left side (71.4%). The main site for the suspicious abnormality was 50% left, 35.7% right and 14.2% bilateral. Our results agree with others where 50% of the effected nodules were left sided [18]. In about 61.5% of our cases, the suspected nodules had complex composition, higher than the 25% reported elsewhere [19]. Regarding nodular vascularity, 60% of our cases had positive doppler flow, (40% intranodular vascularity, 40% perinodular, 20% both). Other research reported inconsistent findings. One study found a 100% positive doppler flow (15% intranodular, 15% perinodular, 70% both) (Brandler et al. 2018) [19]; another observed a 35.6% positive doppler flow (33.3% intranodular, 2.2% perinodular) [20]. As for calcifications, 86.6% of our cases had no calcifications, in agreement that 86% of NIFTP cases were negative for calcifications [18]. On US, all our cases had negative malignant feature of lymph node, supporting two studies that reported 97.6% and 100% negative lymph node metastases respectively [14,20].

The decision for surgery was premised after discussion of the US and FNAC findings at the Thyroid MDT meeting (except Cases 13 and 15 that had US only followed by surgery as the patients were symptomatic). All our patients underwent surgery (60% lobectomy, 40% total thyroidectomy), and the histopathology of the resected specimens were 86.6% NIFTP and 13.3% NIFTP + PMC. PMC is defined as PTC with diameter ≤ 1 cm, and has indolent behaviour, similar to NIFTP [21]. Our 13.3% NIFTP + PMC agree with others where 17.9% of a total of 363 cases were NIFTP + PMC and the authors recommended that this should be treated differently as there is risk of lymph node micrometastases [17].

In terms of pathology, 14 of our 15 cases had preoperative FNAC. The site of the FNAC was based on the recommendation of the radiologist premised on the previous US thyroid that was undertaken. Exceptions were Case 14 (patient had bilateral FNAC) and Case 13 (US showed multinodular goiter (MNG), FNAC was not done). It should be noted that cytological diagnosis of NIFTP cannot be made as the diagnosis can only be rendered after surgical resection and examination of the specimen.

Table 4
Detailed profiles of 15 prospective cases of noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Case/year	Age/sex	Nat	Symp	BMI ^a	TS	LN	SM of Ln	Site by US	FNAC	BC	Site of higher BC	S	FD by HP	Site by HP	PO CTT	PO TG	Final TG
1/2018	41/M	Eg	N	28.73	E	Y	N	L	FLUS	III	L	LO	NIFTP	L	N	10.5	4.9
2/2020	33/F	Eg	Y	26.11	E	N	NAP	L	FLUS	III	L	T	NIFTP+PMC	Bi ^c	LRAI	0.1	0.1
3/2019	52/F	Q	Y	30.36	H	Y	N	Bi	FN + HC & C	IV	R	T	NIFTP	L ^c	N	NA	NA
4/2017	44/F	Q	Y	29.05	E	N	NAP	R	FLUS	III	R	T	NIFTP	R	RAI	10.7	5.8
5/2018	31/F	F	Y	NA	E	Y	N	L	FLUS	III	L	LO	NIFTP	L	T	NA	NA
6/2019	33/F	Eg	Y	45.91	E	Y	N	Bi	C + HC	IV	L	LO	NIFTP	L	N	7.7	NA
7/2019	34/M	Tn	Y	28.32	E	Y	N	L	C	II	L	LO ^d	NIFTP	L	N	5.7	NA
8/2020	38/F	Q	Y	24.61	E	Y	N	R	FN	IV	R	LO	NIFTP	R	N	NA	NA
9/2020	36/F	Eg	N	NA	E	Y	N	L	AC	III	L	LO	NIFTP	L	N	NA	NA
10/2020	57/F	Q	Y	33.21	E	Y	N	R	FLUS	III	R	T	NIFTP	R	N	0.1	0.1
11/2020	42/M	P	Y	27.04	E	Y	N	R	Inadequate	I	R	LO ^d	NIFTP+PMC	R	LRAI+T	1.4	0.1
12/2020	27/M	I	Y	27.34	E	Y	N	R	FLUS	III	R	LO	NIFTP	R	N	NA	NA
13/2021	60/F	Q	Y	28.6	E	N	NAP	—	— ^e	—	—	T	NIFTP	R	N	0.3	0.2
14/2021	52/F	F	Y	29.15	E	Y	N	L	C ^b	II	Bi	T ^d	NIFTP	R ^c	N	0.5	NA
15/2021	43/F	F	Y	24.97	E	N	N	L	FN	IV	L	LO	NIFTP	L	N	NA	NA

AC: atypical cells; BC: Bethesda category; Bi: bilateral; C: colloid; CTT: completion treatment; E: euthyroid; Eg: Egyptian; F: Filipino; FLUS: follicular lesion of undetermined significance; FNAC: fine needle aspiration and cytology; FD: final diagnosis; FN: follicular neoplasm; HC: Hürthle cell type; H: hypothyroid; I: Indian; Ln: lymph node; LN: Lymphadenopathy; LO: lobectomy; LRAI: Low dose radioactive iodine; L: left; N: no; NA: data not available; NAP: not applicable; Nat: nationality; NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; NS: non-specific; P: Pakistani; PO CTT: post-operative completion treatment; PO TG: post-operative thyroglobulin; PMC: papillary microcarcinoma; Q: Qatari; R: right; RAI: Radioactive iodine, dose unknown as it was delivered overseas (Thailand); S: surgery; SM: suspected malignancy; Symp: symptomatic; T: total thyroidectomy; Tn: Tunisian; TS: thyroid status; US: ultrasound; Y: yes; -ve: negative; +ve: positive; —: not done. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC): 6 categories for thyroid cytology reporting [I-nondiagnostic, II-benign, III-atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS), IV-follicular neoplasm/suspicious for follicular neoplasm (SFN), V-suspicious for malignancy, and VI-malignant].

^a Body mass index in kg/m².

^b Patient had ultrasound showing left thyroid lobe nodule with calcifications for which the radiologist recommended FNA from left thyroid lobe, however US guided FNA was done from the 2 lobes.

^c Cases with discrepancies detailed in the discussion section.

^d Three cases underwent surgery despite their low BSRTC category. Case 11 (BSRTC category I) had FNA twice and both cytology samples were inadequate, however MDT recommended lobectomy as patient was symptomatic, Cases 7 and 14 (both BSRTC category II) had lobectomy and total thyroidectomy respectively as both patients were symptomatic and FNAC showed colloid nodule.

^e Case 13 FNAC was not done, surgery was done as patient was symptomatic and US showed MNG.

While aspirates from NIFTP usually yield cellular smears, there is variable expression of nuclear features of papillary carcinoma. Hence, the diagnosis of NIFTP hinges on the histological examination of the post-operative specimen. Four histopathological criteria are required for NIFTP diagnosis: 1) encapsulation or clear demarcation of the lesion from the adjacent thyroid tissue; 2) follicular growth pattern; 3) nuclear features of papillary carcinoma; and, 4) absence of: a) invasion, b) well-formed papillae or psammoma bodies, c) >30% solid/trabecular/insular growth pattern, d) tumor necrosis, e) high mitotic activity, and f) specific variants of papillary carcinoma. Secondary criteria, such as absence of BRAFV600E mutation or other high-risk mutations such as TERT or TP53 are helpful, but not required for diagnosis [12].

The presence of papillary-like nuclear features (criteria 3) has to be scored based on: i) nuclear size and shape (nuclear enlargement/crowding/overlapping and elongation); ii) nuclear membrane irregularities (irregular nuclear contours, grooves, pseudoinclusions); and iii) chromatin characteristics (chromatin clearing with margination, glassy nuclei). At least 2 of the 3 categories must be present at a significant level for NIFTP diagnosis.

NIFTP is a borderline tumor, belonging to a biologically related group of follicular patterned thyroid neoplasms, including follicular adenoma, follicular carcinoma and encapsulated follicular variant of papillary carcinoma. NIFTP is currently considered to be a precursor of invasive encapsulated follicular variant of papillary carcinoma. This is supported by the genetic alterations common to both entities, primarily the point mutations of RAS genes, involving codons 61 and occasionally 12 or 13 of NRAS, HRAS or KRAS genes. BRAFV600E mutations, characteristic of classic papillary carcinoma, are not found in NIFTP, although about 5% of NIFTP carry BRAFK601E mutation. It should be emphasized that none of these molecular alterations are diagnostic of NIFTP, as they are also seen in other follicular patterned neoplasms.

NIFTP is related closely to encapsulated follicular variant of papillary thyroid carcinoma, which usually show invasion and in the rare cases where invasion is not detected, either 30% to 50% solid/trabecular/insular growth pattern or high-grade features are typically found. Distinction between the two is important as the encapsulated follicular variant of papillary thyroid carcinoma exhibits distant metastasis, unlike the NIFTPs. All our cases were diagnosed as per the strict histological criteria mentioned above [22,23].

Many studies have attempted to predict the likelihood that a lesion could be NIFTP by using BSRTC [24,25]. The FNAC results are converted into the BSRTC, comprising 6 categories, each corresponding to risk of malignancy and guide for management [26]. Half of our FNACs were BSRTC category III, 21.4% category II, 21.4% category IV, 7.1% category I, and 0% categories V and VI. A recent meta-analysis found that the NIFTP percentages from surgical resected nodules were 2.2% BSRTC category I, 1.6% category II, 9.5% category III, 10.6% category IV, 15.8% category V, and 2.3% in category VI [27]. Our findings were almost similar to this meta-analysis for categories I, IV, and VI; however, we observed a higher incidence of NIFTP in categories II and III, and less in category V [27]. Hence, we agree with others [27] that the highest percentages of the BSRTC were categories III, however, our data also showed a high percentage of category II.

We observed discrepancy in terms of the US-recommended site for the preoperative FNAC and its resultant diagnosis compared to the site of the histopathology in the resected specimen and its diagnosis. Three of our cases exhibited such discrepancy (Table 4). For instance, for Case 2, FNAC showed left nodule FLUS but histopathology showed bilateral NIFTP + PMC. Likewise, in Case 3, US indicated suspicious nodule in both lobes; FNAC discovered follicular neoplasm with Hürthle cell type (FN + HC) on the right side and colloid on the left; but histopathology confirmed NIFTP on the left side with nodular thyroid hyperplasia. Similarly, in Case 14, US showed a suspicious nodule on the left side, but the final histopathology was NIFTP on the right side. Such discrepancies suggest that NIFTP might sometimes be incidentally diagnosed, regardless of the US or FNAC findings. Given that the term NIFTP

indicates an indolent course and prevents over-treatment [11], this in turn raises questions about the extent of NIFTPs potentially missed by US/FNAC workups, further compounded by non-resection that would prevent histopathological confirmation. Hence it seems plausible that the true incidence of NIFTP might remain underestimated. Future research could appraise ways to improve US/FNAC workups in discovering NIFTP.

Regarding size, the mean NIFTP size was 2.1 ± 1.75 cm, which concurs with other studies where the mean sizes ranged from 2.18 ± 1.47 cm to 2.5 cm [16,17]. For NIFTP reaching 4–5 cm, most surgeons are anxious in treating them conservatively [28]. Regarding the number of foci, 86.6% of our cases were unifocal and 13.3% were multifocal, where others found 31.5% of NIFTP cases were multifocal [29].

Moreover, after MDT discussions, patients who had NIFTP + PMC underwent completion treatment. For instance, Case 2 had total thyroidectomy that was completed by RAI; and Case 11 had lobectomy, which was then followed by completion surgery and RAI, as surgery is the mainstay treatment of PMC [30]. Case 4 had RAI as her post-operative TG level was high (10.7 ng/ml) which then decreased to 5.8 ng/ml.

As for follow up, patients were followed up with serum thyroglobulin and neck US, in line with the guidelines of the American Thyroid Association [30]. Our mean postoperative thyroglobulin was 4.56 ± 4.95 ng/ml as our cases underwent a mix of total thyroidectomy and lobectomy. On follow up, as some patients had additional completion treatment, the mean level decreased to 2.8 ± 3.14 ng/ml. Nevertheless, our recurrence and metastases data are limited as most of our patients were diagnosed in 2020 (Table 1) and 1 patient was lost to follow up (Case 5).

6. Conclusion

This report is possibly the first to elaborate quantitatively and qualitatively on 15 prospective NIFTP cases diagnosed postoperatively. Discrepancies are not uncommon in NIFTP in terms of the US-recommended site for the preoperative FNAC and its resultant diagnosis compared to the site of the histopathology in the resected specimen and its diagnosis. Such discrepancies suggest that NIFTP could be deceiving in its diagnosis, or might sometimes be incidentally diagnosed, regardless of the US or FNAC findings. Hence, surgeons might need to maintain an index of suspicion to negative, benign, or inconclusive US or FNAC findings among symptomatic females with high BMI. To date, NIFTP is diagnosed post operatively, hence it is possible that the true incidence of NIFTP might remain underestimated. Future research is needed to predict preoperative diagnosis of NIFTP and explore the relationships between between BMI and NIFTP. NIFTP reports from the Middle East and North Africa region are scarce; surgeons should be encouraged to publish such cases.

Sources of funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Ethical approval

Approved by Medical Research Center, Hamad Medical Corporation IRB (MRC# 04-21-906).

Consent

For publication of this case series and accompanying images, written informed consent was obtained from 7 patients; copies of the signed consents are available for review by the Editor-in-Chief of this journal on request. Verbal consent was obtained from 4 patients over the telephone from the patients after through explanations of the fact that the cases will be published in a scientific journal without breaking confidentiality

or disclosing identity; the discussions were witnessed by a co-author. Three cases could not be reached after multiple attempts, and one case had travelled outside of the country. The head of our team has taken responsibility that exhaustive attempts have been made to contact these patients or their families and that the paper has been sufficiently anonymized not to cause harm to the patients or their families.

CRediT authorship contribution statement

Mohamed S Al Hassan: Writing - review & editing. Walid El Ansari: study concept, data interpretation, writing the paper, review & editing. Hamzah El Baba: data collection, data interpretation, writing the paper, review & editing. Mahir Petkar: Laboratory data, Writing - review & editing. Abdelrahman Abdelaal: study concept, Writing - review & editing. All authors read and approved the final version.

Research of registration

Not first in man.

Guarantor

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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