Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in pediatrics

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ABSTRACT

Introduction. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has a low malignancy potential. First acknowledged by the WHO in 2017, this tumor is rare in the pediatric population, with less than 25 cases reported. Accurate diagnosis is key to avoid overtreatment and complications.

Clinical observation. Two cases of adolescents with solid thyroid nodules assessed by fine-needle aspiration biopsy are presented. Hemithyroidectomy was decided upon. Both surgical specimens were reported as NIFTP. Both cases were presented before a cross-disciplinary board, and since malignancy potential was low, treatment was regarded as completed.

Discussion. NIFTP identification is key to avoid unnecessary treatments such as total thyroidectomy or iodine therapy, which may bring about serious consequences in children. A high level of diagnostic suspicion and a cross-disciplinary approach are required to optimize management and clinical results in these patients.

KEY WORDS: Thyroid neoplasms; Thyroidectomy; Pediatrics; Neoplasms by histologic type.

NEOPLASIA FOLICULAR TIROIDEA NO INVASIVA CON CARACTERÍSTICAS NUCLEARES DE TIPO PAPILAR (NIFTP) EN PEDIATRÍA

RESUMEN

Introducción. La neoplasia tiroidea folicular no invasiva con características nucleares de tipo papilar (NIFTP) es un tumor de bajo potencial maligno, reconocido por la OMS desde 2017. Es poco frecuente en la población pediátrica, con menos de 25 casos reportados. Su diagnóstico preciso es clave para evitar el sobretratamiento y sus complicaciones.

Observación clínica. Se presentan dos casos de adolescentes con nódulos tiroideos sólidos evaluados mediante biopsia por aspiración con aguja fina. Se decidió realizar hemitiroidectomía. La patología de ambas piezas quirúrgicas reportó NIFTP. Se presentaron los casos en junta multidisciplinaria y en fundamento a su bajo potencial maligno se estableció como completo el tratamiento realizado.

Comentarios. El reconocimiento de la NIFTP es esencial para evitar tratamientos innecesarios como la tiroidectomía total y la yodoterapia, que pueden tener consecuencias significativas en niños. Se requiere una alta sospecha diagnóstica y un enfoque multidisciplinario para optimizar el manejo y los resultados clínicos en estos pacientes.

PALABRAS CLAVE: Neoplasias tiroideas; Tiroidectomía; Neoplasias por tipo histológico.

INTRODUCTION

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has a low malignancy potential. First acknowledged by the WHO in 2017[1], this tumor is associated with unspecific clinical signs and no compression symptoms, and is often incidentally identified at neck ultrasonography[2]. Diagnosis requires histological confirmation, since it can be mistaken for thyroid papillary cancer (TPC). NIFTP-related knowledge primarily stems from adult studies as it is a rare condition in children. Prognosis in the pediatric population is favorable, with high survival and low recurrence rates. Hemithyroidectomy without iodine therapy is recommended to treat these cases[3-6]. This paper presents two pediatric NIFTP cases and describes management and clinical and surgical results. It also features a literature review in patients under 18 years of age.

CLINICAL OBSERVATION

Case 1

17-year-old female patient referred to our department as a result of a large left hemineck, without pain or lymphadenopathy. Thyroid ultrasonography revealed a 57×40 mm homogenous nodular injury, without calcifications, with central and peripheral vascularization, categorized as TI-RADS 4. The thyroid profile showed slightly high TSH levels and normal free T4 levels. The fine-needle aspi-

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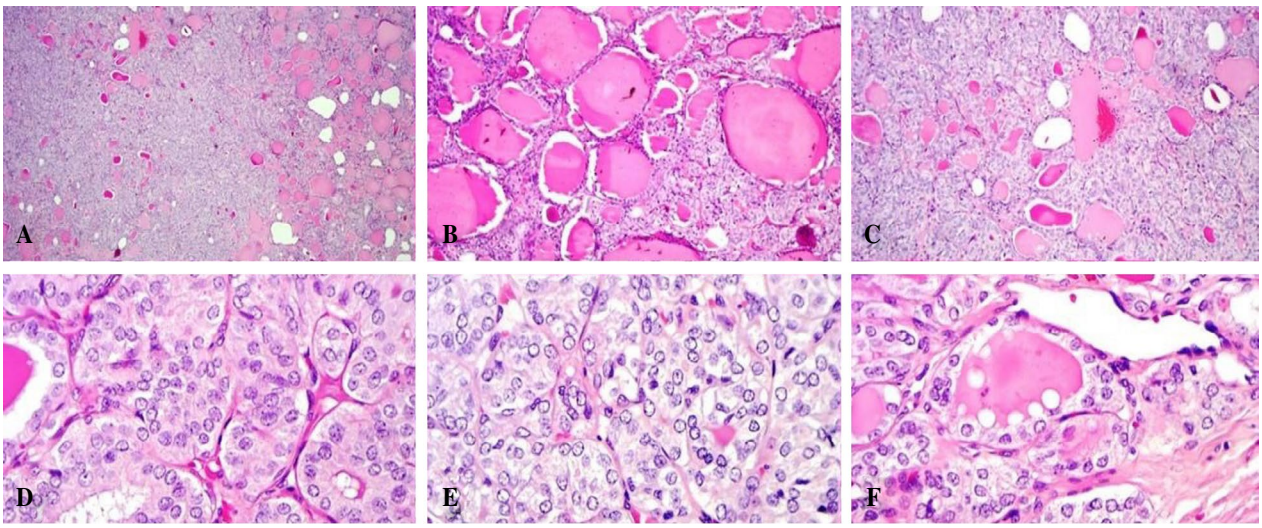

Figure 1. Left hemithyroidectomy, histology. Hematoxylin-eosin staining. A) and B) Thyroid parenchyma compromised by a well-delimited neoplasm, with no capsule surrounding it. The limit between the normal parenchyma and the neoplasm is obvious (40x). C) Primarily consisting of variable sized follicles, with variable intraluminal colloid (100x). D) to F) The nuclei of neoplastic cells are enlarged, with crowding, superposition, grooves, clearing, and pseudo-inclusions (400x). E) No papillae, psammoma bodies, high cells, vascular invasion, or necrosis were observed.

ration biopsy (FNAB) result was labeled as Bethesda V, suggesting a malignant papillary neoplasm. Considering the ultrasound characteristics of the nodule and given that benignity chances were 30%, a left hemithyroidectomy was carried out. The surgical specimen demonstrated a solid, well-delimited tumor in close contact with the capsule, without adjacent tissue invasion, follicular pattern growth, or formation of papillae and nuclei with grooves and nuclear clearing (Fig. 1). Histopathological diagnosis was NIFTP.

Case 2

11-year-old patient referred to our department as a result of a right thyroid nodule. T3 levels were high, and ultrasonography revealed a 22×23 mm solid cystic nodule (TI-RADS 3) with increased uptake at scintigraphy. Considering thyroid profile, ultrasonography, and thyroid scintigraphy results, clinical follow-up was decided upon, with ultrasonography and thyroid profile. After a one-year follow-up, the nodule increased in size and was catalogued as Bethesda V at FNAB. The patient underwent a right hemithyroidectomy. The pathology report showed a well-delimited tumor with a bleeding center, no adjacent vascular or lymphatic tissue invasion, no necrosis, and papillary nuclear features. Histopathological diagnosis was NIFTP.

The cases were assessed by a cross-disciplinary board. Given the low malignancy potential of NIFTP and its non-aggressive behavior, the treatment was regarded as complete, with no total thyroidectomy or iodine therapy required. After a 12-month follow-up, no clinical, serum, or imaging relapse signs have been observed.

The characteristics of the two NIFPT cases reported in this series are featured in Table 1. All cases previously reported in the English-speaking literature (n= 22) were included for total analysis purposes (n= 24). Based on NIFTP data in pediatrics, most cases were female (62.5%), with a mean age of 14.4 years at diagnosis. Tumor size ranged from 0.95 to 5.7 cm, with a mean of 2.3 cm. Regarding preoperative FNAB results, Bethesda IV was the most common category, with a total of 6 patients (33.3%), followed by Bethesda V, with a total of 5 patients (27.8%), Bethesda III, with a total of 4 patients (22.2%), and Bethesda II, with a total of 3 patients (16.7%). All patients underwent surgical management (n= 24/100%). 18 children went through total thyroidectomy (75%), 3 patients underwent hemithyroidectomy (12,5%), and thyroidectomy was completed in 3 patients (12.5%). Only 2 patients received adjuvant iodine therapy. The 24 cases are currently free from recurrence or metastatic disease, with follow-up periods ranging from 12 months to 7 years. It is worth noting that all cytopathological studies were classified as Bethesda V, with no intermediate categories.

DISCUSSION

With some 567,000 cases annually, thyroid cancer is the ninth most common cancer type in adults. However, it is rare in children, since it accounts for only 0.7% of cancers in patients under 18 years of age. In adolescents aged 15-19 years old, it is the eight most frequent type in male patients and the second in female patients, with a prevalence of 4:1-6:1[7-10]. Most cases are differentiated

Table 1. Demographic and clinical and pathological characteristics of all NIFTP cases reported (n= 24, including the two cases from this series).

Case	*Age*	*Category/FNAB*	*Surgery*	*Tumor size (cm)*	*Iodine therapy*	*Follow-up*	*Reference*
1	17/F	V	Hemithyroidectomy	5,7	No	12 months	This series
2	11/M	V	Hemithyroidectomy	2	No	12 months	This series
3 to 5	MA= 16.7; F:M= 2:1	II, III, III	Total thyroidectomy (1), Thyroidectomy completion (2)	1.9 (mean)	Yes (1), No (2)	> 2 years	Wang et al.[5]
6 a 11	MA= 14.4; F:M= 2:1	II (1), IV (2), V (1), N/A (2)	Total thyroidectomy (4), Thyroidectomy completion (1)	0.95 (mean)	Yes (1), No (5)	> 1 year	Halada et al.[6]
12 a 15	MA= 15; F:M= 3:1	III, IV, V, N/A	Total thyroidectomy	1.4 (mean)	No	> 1 year	Mariani et al.[13]
16	10/F	III	Total thyroidectomy	2	No	> 1 year	Abdou et al.[17]
17 to 20	MA= 13; F:M= 3:1	II (1), IV (2), V (1)	Total thyroidectomy	2 (mean)	No	> 2 years	Rosario et al.[18]
21 & 22	MA= 14; F:M= 1:1	N/A	Total thyroidectomy	NA	No	> 1 year	Samuels et al.[19]
23 & 24	< 19; F:M= N/A	IV	Total thyroidectomy	NA	No	> 7 years	Rossi et al.[20]

F = female; M = male; MA = mean age; N/A = not applicable.

thyroid cancer, with the papillary variant being the most frequent one (90%)[10,11].

NIFTP is a rare thyroid neoplasm in children, with less than 25 cases reported. It belongs to a group of well-delimited, low malignancy potential tumors known as "borderline." They are not invasive, and the risk of recurrence or metastasis is minimal[14]. Clinical presentation is typically a thyroid nodule, similar to differentiated thyroid cancer[2]. In children, malignancy suspicion is greater, since 22-26% of solitary nodules are malignant vs. 5-14% in adults[10]. Therefore, current pediatric guidelines by the American Thyroid Association (ATA) recommend the use of FNAB for vascular, calcified, solid, and/or pericapsular nodules according to the clinical context, not only their size[11,12].

In NIFTP, FNAB cytopathological results range from categories II to V, with category IV being the most frequent one (42%). Definitive diagnosis is established based on the analysis of the surgical specimen, which should be differentiated from thyroid papillary cancer (TPC) and other more invasive malignant neoplasms[5,13,14]. Histopathological criteria were described by Nikiforov et al. in 2016, and NIFTP was included in the WHO's classification of endocrine tumors in 2017. Table 2 summarizes inclusion criteria for NIFTP diagnosis. At the molecular level, it typically presents with RAS mutations, but no BRAF or PPARG ones[1-3].

Even though diagnostic criteria have been clearly established, the preoperative diagnosis of NIFTP remains challenging. Diagnostic criteria are based on histology, since the accuracy of FNAB-based NIFTP diagnosis and ultrasound findings are variable. According to Mariani et al., the specificity of FNAB for follicular thyroid neoplasms is low (66%) in children, and up to one third of NIFTP cases are classified as malignancy-suspect (Bethesda V)[13].

Table 2. Inclusion criteria for non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)[5,12,13].

Cytomorphology	*Histology*
– Predominance of micro-follicles – Nuclear enlargement, elongation, and superposition – Nuclear pseudo-inclusions – Irregular contours – No psammoma bodies	– Predominantly follicular pattern – Encapsulated or well-delimited – No vascular or tumor capsule invasion – If solid, trabecular, or insular pattern: the total should be less than 30 % of tumor volume – High mitotic activity

Given the risk of second neoplasms and pulmonary fibrosis as a result of iodine therapy, the treatment of thyroid papillary cancer (TPC) is now more conservative as it considers both the control of the disease and the sequelae of total thyroidectomy and iodine therapy[13]. In this case series, hemithyroidectomy was decided upon, since up to 30% of cases classified as Bethesda V were considered to be potentially non-malignant[11]. If differentiated thyroid

cancer happened to be confirmed, thyroidectomy would be carried out in a second maneuver. However, the pathological result revealed the presence of NIFTP, thus avoiding an unnecessary radical surgery and its complications. Since it is not regarded as a carcinoma, NIFTP does not require an aggressive treatment or entail a psychological, economic, and social impact as big as cancer. This "less is more" approach places great importance on surveillance and close follow-up in patients with low-risk tumors[13].

There is currently no standardized follow-up protocol in NIFTP patients. Generally speaking, clinical and imaging follow-up with neck ultrasonography, as well as serum follow-up measuring thyroglobulin and anti-thyroglobulin antibodies, is proposed both in adults and in patients under 18 years of age.

Most NIFTP studies are based on adults, with pediatric evidence being limited. This is the first pediatric report in Latin America. Identification is crucial to avoid overtreatment and complications. Understanding NIFTP behavior allows for adequate management, thus reducing the risk of radical surgeries and unnecessary treatments such as iodine therapy. Multi-center studies in patients under 18 years of age are required to improve detection and comprehension.

In conclusion, NIFTP is rare in adults and even more in children. Identification prevents overtreating a non-aggressive neoplasm and potential overtreatment consequences. Accurate diagnosis and a cross-disciplinary approach are key to optimize management and outcomes in these patients.

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