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Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): Update and Diagnostic Considerations—a Review

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Abstract
Advances in our understanding of thyroid lesions, especially those entities with an indolent behavior, has led clinicians to question the most appropriate surgical management of such thyroid nodules. Several studies have shown that the non-invasive encapsulated follicular variant of papillary thyroid carcinomas (NI-EFVPC) exhibits poor histopathologic diagnostic reproducibility and have been over-treated as conventional thyroid cancer. In 2015, an international thyroid working group re-evaluated NI-EFVPC and its diagnostic criteria. The new terminology of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was accordingly introduced to replace NI-EFVPC. The literature has emphasized that NIFTPs are biologically similar to follicular adenomas lacking lymph node metastases and/or recurrence. While the definition of NIFTP is based on specific morphological parameters, recent studies have questioned whether the criterion allowing less than 1% of true papillae should be revised to a total absence of papillae. The motivation for this revision is the rare finding, in some studies, of lymph nodes with metastatic NIFTP. This review evaluates the existing published series of NIFTP cases, clinical consequences of NIFTP, and emerging changes in the diagnostic criteria for NIFTP. The introduction of NIFTP has resulted in significant impact on the clinical management of thyroid nodules. Recent revisions in the morphological criteria for NIFTP emphasize the need to adhere to very stringent histomorphologic criteria when making a diagnosis of NIFTP. The adoption of NIFTP terminology instead of NI-EFVPC is associated with conservative lobectomy without radioactive iodine treatment in the majority of cases.

Keywords Papillary thyroid carcinoma · Follicular variant of PTC · NIFTP · Thyroid cytology · Molecular testing · Personalized medicine

Introduction

In recent decades, the incidence of thyroid carcinoma, including small nodules, has nearly tripled even though no change in mortality has been reported [1–3]. In fact, increased screening employing radiologic modalities and the use of fine needle aspiration (FNA) in the evaluation of thyroid nodules have resulted in the detection of subcentimeter malignant nodules. This approach has led to the conclusion that most thyroid tumors are likely indolent and being overtreated. Among them was the follicular variant of papillary thyroid carcinoma (FVPTC) [4–11]. FVPTC comprises 9 to 22% of papillary thyroid carcinomas (PTCs), including neoplasms with encapsulated or infiltrative features, which differ prognostically and in their respective molecular profiles [7–12]. The infiltrative FVPTCs (I-FVPTC) are associated with a higher risk of recurrence, frequent lymph node metastases, and mutations in $BRAF^{V600E}$, whereas one-third of encapsulated FVPTC (E-FVPTC) especially those lacking any invasive characteristics

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(NI-EFVPTC) do not show lymph node metastases, $BRAF^{V600E}$ mutations and do not recur locally or at distant sites [5]. Nevertheless, NI-EFVPTC continued to be diagnosed as "carcinoma" resulting in psychosocial stigmata, over-treatment such as total thyroidectomy, and radioactive iodine (RAI) [4, 6–14].

The Endocrine Pathology Society working group (ESP-WG) reviewed a large series ($n = 268$) of NI-EFVPTCs and concluded that the absence of invasion was associated with indolent biologic behavior, similar to follicular adenomas, even when patients were treated conservatively with thyroid lobectomy or without RAI [10]. Thus, the ESP-WG proposed a new diagnostic term, the "noninvasive follicular thyroid neoplasm with papillary like nuclear features" (NIFTP), which underscores the key features of this indolent thyroid neoplasm. The reclassification of NI-EFVPTC as NIFTP had important implications for the cytological interpretation of thyroid nodules as it significantly impacts the risk of malignancy (ROM) for the diagnostic categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [12–18].

This review highlights the clinicopathological specifics of NIFTP and discusses the recently proposed revisions of diagnostic criteria for NIFTP [19] as well as the impact on patient management.

Methods

A literature search was performed to identify studies published in English that analyzed the rate of NIFTP with surgical follow-up since its introduction in April 2016 [10]. The following resources were employed for systematic data collection: the electronic databases from PubMed, Scopus, and Web of Science. Searches used the keywords [Thyroid] AND [Carcinoma, neoplasm, cancer or nodule] AND [NIFTP] AND [follicular variant of PTC]. Evaluation of various journal websites and references of previous review articles were also employed.

Results

Of 118 retrieved references, 42 were retained and their full text was assessed. The majority of the studies included retrospective series. Included studies were published by authors from the USA, Canada, Europe, and Asia. The majority of these studies reported cases of histologically proven NIFTP. Extracted data included: (i) number of thyroid carcinoma cases; (ii) number of PTC, FVPTC, I-FVPTC, and NIFTP cases with follow-up; and (iii) number of NIFTP cases with $\leq 1\%$ papillae. An additional search for the recent revision of NIFTP morphological criteria was conducted using PubMed.

Discussion

Pathology

For the past four decades, nuclear features of thyroid follicular cells have been considered the most reliable morphological criteria to diagnose PTC [20–26]. In fact, these nuclear features in thyroid lesions trump the architectural features such as the presence or absence of a tumor capsule, invasive characteristics, or papillary architecture. The FVPTC was described in the mid-1970s as a tumor with a predominant follicular growth pattern and concomitant nuclear features of PTC. Following this, two subtypes of FVPTC were recognized: infiltrative (I-FVPTC) and encapsulated (E-FVPTC) forms; the latter can be invasive or non-invasive [24–29]. While I-FVPTC frequently metastasizes to cervical lymph nodes similar to classical PTC, E-FVPTC behaves in a more indolent fashion especially when there is no capsular or vascular invasion (NI-EFVPTC). The variable morphology and clinical course of these subtypes of PTC caused controversies in the diagnosis and management of E-FVPTC, especially for NI-EFVPTC. The confusion was accentuated by a lack of uniform criteria to diagnose E-FVPTC even among endocrine pathology experts. Several publications, including some with lengthy clinical follow-up, emphasized that NI-EFVPTC behaved in a benign manner and that the majority of these cases were overtreated. This argument was further strengthened by the knowledge provided by molecular profiling which showed that I-FVPTC and E-FVPTC (including both invasive and non-invasive entities) have a unique set of gene mutations and fusions. In order to resolve this controversy, the ESP-WG recommended that NI-EFVPTC be re-defined as a neoplasm rather than carcinoma and consequently be termed NIFTP [10]. This was intended to lessen the clinical and psychological implication related to the over-diagnosis of this lesion as "cancer," as well as reducing comorbidity associated with overtreatment.

Clinical Presentation

NIFTP presents similarly to most thyroid nodules that are detected on physical examination or by imaging. Ultrasound findings are typically those of a well-circumscribed oval/round nodule that is hypervascular with a hypoechoic rim, compared to I-FVPTC which have more irregular or lobulated margins and are mostly hypervascular [Fig. 1a; [30]. The ultrasound of I-FVPTC also shows at least one suspicious feature for malignancy including marked hypoechogenicity, microcalcifications, blurred margins, "taller than wide" nodule, and a mostly avascular color Doppler pattern [30].

Since the introduction of NIFTP, several studies have provided insight into the impact of this new terminology on the interpretation of thyroid fine needle aspiration (FNA) [9,

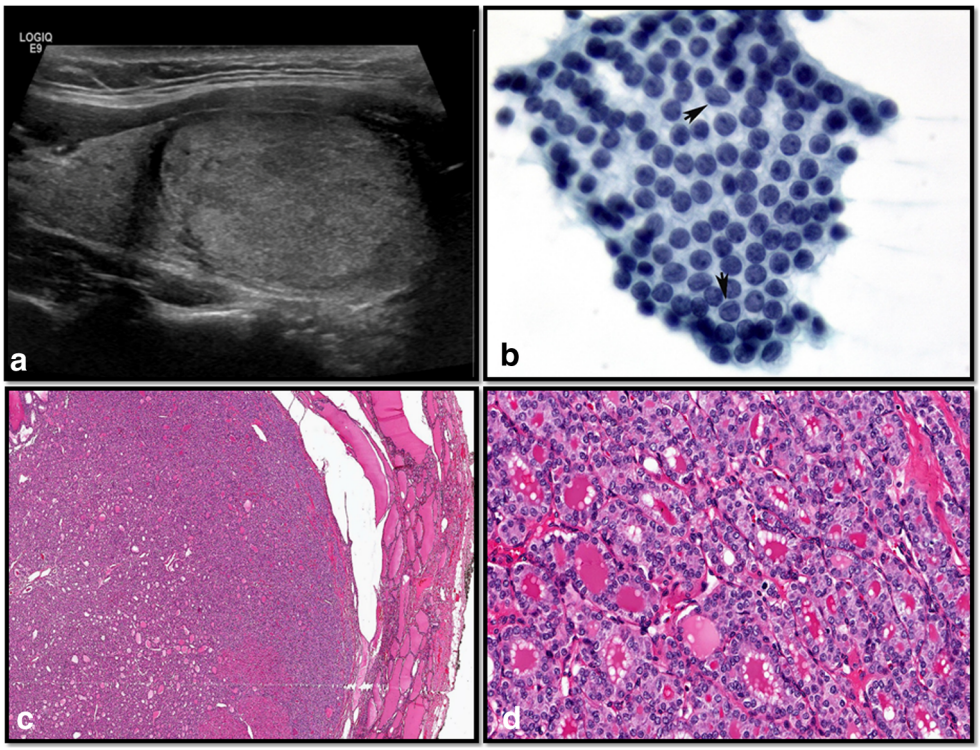

Fig. 1 Ultrasonographic, cytomorphologic, and histopathologic features of a case of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). **a** The ultrasound examination showed a solid isoechoic nodule; cytological smear stained with Papanicolaou stain shows a monolayer sheets of follicular cells containing elongated nuclei with nuclear chromatin pallor, intranuclear grooves (arrows), and eccentrically placed nucleoli. **b** The case was diagnosed as suspicious for malignancy based on the morphological features (conventional Pap smear, × 400). **c** The histopathologic evaluation demonstrated a well-demarcated follicular-patterned nodule without invasive characteristics (H&E × 200), and **d** cells lining the follicles show nuclear features diagnostic of papillary thyroid carcinoma (H&E × 400)

12–18, 31–35]. If NIFTP was classified as a non-malignant lesion, the risk of malignancy (ROM) in each diagnostic category of TBSRTC would be reduced, particularly for nodules classified as indeterminate [9, 12–18]. Several studies compared the cytological features of NIFTP to classical PTC and/or FVPTC [9, 12–18, 31–35]. These studies confirmed that the majority of NIFTP cases belong to TBSRTC categories III, IV, and V (Fig. 1b), and that three cytomorphological features (namely microfollicular pattern, lack of papillary structures, and intranuclear pseudoinclusions) are helpful to predict a possible NIFTP diagnosis on a subsequent surgical pathology specimen (Fig. 1b). Unfortunately, these cytomorphological features cannot reliably distinguish NIFTP from FVPTC, and at present, the majority of NIFTP cases are frequently diagnosed as indeterminate or suspicious for malignancy [Fig. 1b; [36–40].

Recently, some authors have reported NIFTP cases that were associated with loco-regional micrometastases, as well as *BRAF*^{V600E} mutation and/or *BRAF*-like mutation (*RET/PTC* rearrangement) or high-risk *TERT* promoter mutations [19, 24–29]. Hence, substituting the criterion of "less than 1% papillary structures" with "no well-formed papillary structures" has been proposed, along with pathologic examination of the entire nodule, especially in the presence of florid nuclear features of PTC (nuclear score 3) by a subset of the original consensus group. A comparison between the initial diagnostic criteria and current revised criteria is displayed in Table 1.

Assessment and Diagnosis

As reported by Nikiforov et al. in the seminal paper describing NIFTP, the histological diagnosis of NIFTP is rendered by strictly adhering to inclusion and exclusion morphological criteria [10]. The key parameters include nuclear cytology of PTC (i.e., nuclear membrane irregularities, ground glass appearance of nuclei, and large nuclear size) in the setting of a non-invasive follicular-patterned tumor (Fig. 1c, d). The presence of an exclusive follicular growth pattern and lack of any invasive characteristics is of paramount importance in the diagnosis of NIFTP. Complete histological evaluation of the entire tumor capsule and careful examination to exclude any papillary architecture tops the list of inclusion criteria. While the original paper by Nikiforov et al. advocated the presence of < 1% papillary structures, a recent study by Cho et al. demonstrated that even the presence of 1% papillae can be associated with lymph node metastases [27]. Therefore, in a

Table 1 Comparison of NIFTP diagnostic criteria before and after proposed revisions

	Original diagnostic criteria[10]	Revised diagnostic criteria[19]
Encapsulation or clear demarcation		
	X	X
Follicular growth pattern	X	X
< 1% papillary structures	X	
No well-formed papillae	X	X
Nuclear features of PTC	X	X
No psammoma bodies	X	X
Nuclear features	X	X
Score 2–3	X	X
Nuclear elongation/grooves/chromatin clearing	X	X
< 30% solid/trabecular/insular growth pattern	X	X
No vascular and capsular invasion	X	X
No tumor necrosis	X	X
No high mitotic activity	X	X
Lack of *BRAF*^{V600E} mutation with IHC or molecular testing	X	X
Lack of *BRAF-like* mutations or other high-risk mutations (*TERT and TP53*)	X	X

PTC, papillary thyroid carcinoma; *IHC*, immunohistochemistry; *X*, inclusion criteria

[#] Partially adapted from a table by Rossi ED and Faquin WC in Cancer Cytopathology 2018 [41]

follow-up review by a subset of the NIFTP working group, a recommendation was made that no papillary structures should be allowed in thyroid nodules diagnosed as NIFTP [19]. Concerning papillary structures and their definition, the detection of well-formed papillary structures thus cannot be present to make a definitive diagnosis of NIFTP. A papillary structure is a thin, delicate fibrovascular core covered by neoplastic thyroid follicular epithelial cells that show the nuclear features of papillary carcinoma. Abortive papillae do not contain a fibrovascular core and are just stacked or piled up nuclei. Follicles within a fibrovascular core space are also not true papillary structures. A papillary structure should also have at least three cells on each side surrounding a fibrovascular core. While this may be arbitrary, only 1 or 2 cells on either side are more abortive than true papillae. While papillary structures can be sought at a × 20 magnification, careful high-power examination is also required.

Concerning the nuclear features of PTC, Nikiforov et al. proposed the presence of six features to be grouped into three categories including: (1) size and shape (nuclear enlargement/overlapping/crowding); (2) nuclear membrane irregularities (irregular contours), intranuclear grooves, and pseudo-inclusions; and (3) chromatin characteristics (clearing with margination/glassy nuclei). These nuclear features can be focal or diffuse with some gradation permitted in different areas of the lesion [10]. These features are to be analyzed employing a 3-point scoring scheme in which each class of nuclear features receives a score of 0 or 1, yielding a range from 0 to 3. This scoring scheme demonstrated high sensitivity (98.6%), specificity (90.1%), and diagnostic accuracy (94.3%). The more recently revised criteria emphasize that NIFTP usually exhibits a score of 2 (moderately expressed nuclear features of PTC) and that in cases of NIFTP with a nuclear score of 3, the entire tumor should be evaluated in order to exclude the presence of papillary structures [19]. The working group still maintained the following exclusion criteria: (1) presence of psammoma bodies, (2) tumor necrosis or high mitotic activity, and (3) presence of any lymphovascular invasion and/or lymph node metastases.

Albeit limited, so far, several specific genetic alterations have been associated with NIFTP (Table 2). In many NIFTP cases, a *RAS* mutation is the most typical genetic alteration detected, similar to those found in follicular adenomas and follicular carcinomas. Of note, Howitt et al. [8] found *RAS* mutations in 46% of E-FVPTC while Rivera et al. [42] found that 0% of E-FVPTC and 26% of I-FVPTC have a *BRAF* mutation. Zhao et al., comparing NIFTP with I-FVPTC, reported one case of NIFTP with a *BRAF*^{V600E} mutation whereas 36% of I-FVPTC were *BRAF* mutated [18]. *BRAF*^{V600E} is a prototypic mutation found in PTC and is not expected to be seen in encapsulated follicular-patterned neoplasms, including NIFTP. The majority of studies discussing the genetic alterations in NIFTP demonstrated that *BRAF*^{V600E} was wild type. Nonetheless, 5% of NIFTP harbor a *BRAF*^{K601E} mutation having a different signaling and gene expression signature, which

Table 2 Overview of the most frequent molecular changes seen in NIFTP compared to FA, PTC, E-FVPTC, and I-FVPTC

Testing method	FA	NIFTP	cPTC	E-FVPTC	I-FVPTC
Immunohistochemistry					
HBME-1	–	+	++	+/++	++
GALECTIN-3	–	+	++	+/++	++
CD56	+/++	–	–	–	–
Molecular testing					
BRAF^{V600E}	–	+*	++	+	+
BRAF^{K601E}	+	+	+	++	+
NRAS	++	++	+	++	++
HRAS	++	++	+	++	+
KRAS	++	+	+	++	+
PTEN	++	–	+	–	–
TERT	–	+*	+	+	+
RET/PTC	–	+*	++	+	+
PAX8/PPARγ	+	++	++	++	++
ALK fusion	–	–	+	–	–
BRAF fusion	–	–	+	–	–
ETV6/NTRK3	–	–	++	–	–
NTRK1/3 fusion	–	–	+	–	–
GEC/GSC	Mostly benign	Mostly suspicious	Frequently suspicious	Frequently suspicious	Frequently suspicious

FA, follicular adenoma; *NIFTP*, non-invasive follicular thyroid neoplasm with papillary-like nuclei; *cPTC*, classical variant of PTC; *E-FVPTC*, encapsulated follicular variant of PTC; *I-FVPTC*, infiltrative follicular variant of PTC; *GEC/GSC*, gene expression and gene sequencing classifier;

+Sometimes present

++Commonly present

−Absent

*The detection of these genetic alterations should trigger an exhaustive search for invasive features and papillary formations

is closer to that of RAS mutation. However, single cases of mutated BRAF^{V600E} have been described suggesting that the discrepancy might be due to inappropriate application of the diagnostic criteria for NIFTP. It remains to be determined if BRAF^{V600E} represents an exclusion criterion. Other point mutations and gene fusions have also been linked with NIFTP. *EIF1AX* mutations are found in 5 to 10% of NIFTP and frequently coexist with RAS mutations. Also, mutations affecting the PTEN gene can be found in 5% of NIFTP. Young patients with NIFTP also show *DICER1* mutations in 5% of cases. A higher percentage of NIFTP (20 to 30%) may show either *PAX8/PPARG* fusion or *THADA* fusion. According to the recent revision of NIFTP, the application of molecular testing can be used as a secondary criterion (Table 2 and Fig. 2).

Treatment

Few studies have evaluated the treatment and clinical outcome of NIFTP. The majority of these publications emphasized the indolent outcome in E-FVPTC [41, 43–49]. Ghossein et al. reported in their series that all 78 patients with E-FVPTC were alive and free of recurrence after 11 years compared with 6% of individuals with I-FVPTC [9]. The pivotal paper by Nikiforov et al. confirmed that none of the 109 patients diagnosed with NIFTP had any disease recurrence at follow-up after 10–26 years, while 12% with I-FVPTC experienced recurrences [10]. The introduction of NIFTP accordingly supported conservative management (i.e., lobectomy alone) as well as avoiding any subsequent radioactive iodine therapy [41, 50–52]. The American Thyroid Association (ATA) strongly suggests that well-differentiated thyroid cancers are followed-up by means of serial serum thyroglobulin measurements, serum thyroid stimulating hormone (in patients receiving thyroid hormone therapy), and neck ultrasound [20]. This approach has been adopted for NIFTP [50–54]55]. With NIFTP now associated with the lowest point in the "risk stratification" of thyroid neoplasms, there are consequently fewer emotional and financial consequences to patients with this diagnosis.

Prognosis

As underlined in the original study and endorsed by different publications and Endocrine Societies, NIFTP is defined as a

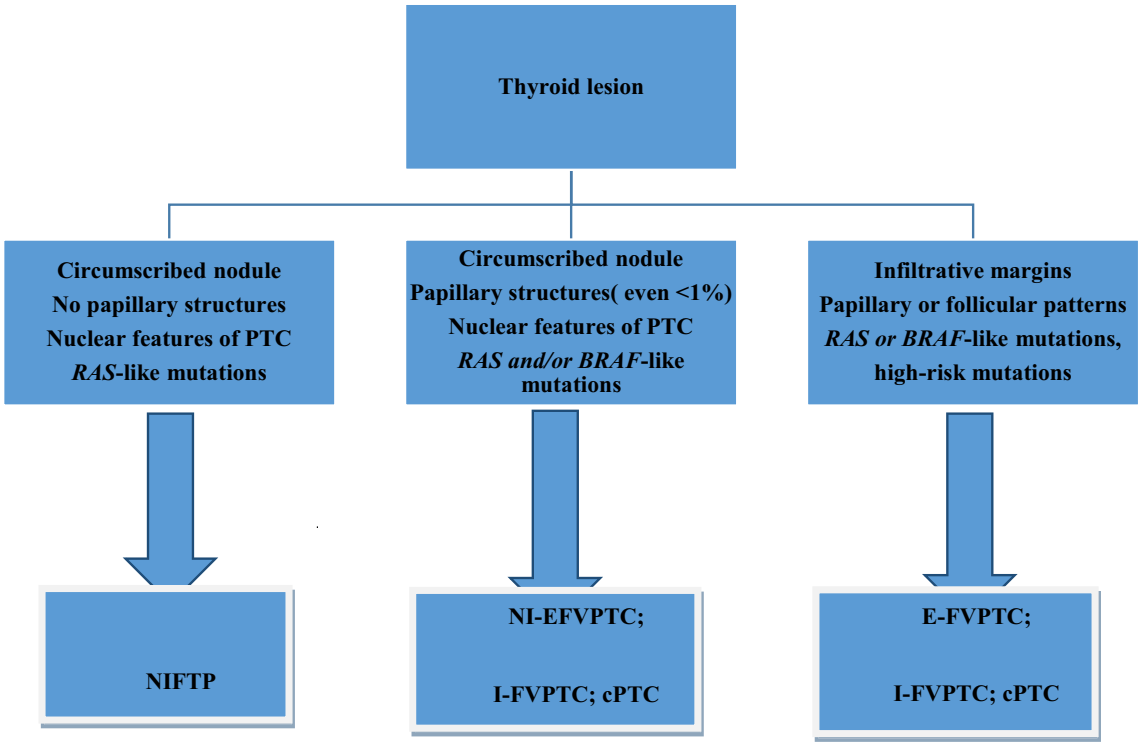

Fig. 2 Diagnostic algorithm approach for NIFTP using revised morphological criteria. Legend: cPTC, classic variant of papillary thyroid carcinoma; NI-FVPTC, noninvasive-encapsulated follicular variant of PTC; E-FVPTC, encapsulated follicular variant of PTC; I-FVPTC, infiltrative follicular variant of PTC

tumor with indolent behavior and an excellent prognosis [19]. Since its introduction, authors such as Cho et al. have reported a few cases presenting with recurrences and/or distant metastases [27]. In those cases, strict adherence to the diagnostic criteria may not have been used. To date, there remain several issues that have yet to be answered such as how to manage subcentimeter lesions, lesions larger than 4 cm, and lesions with an oncocytic component that fulfill diagnostic criteria of NIFTP [25]. Of note, E-FVPTC with oncocytic features seems to at least share the same favorable clinical course as their non-oncocytic counterparts.

Conclusions

The introduction of NIFTP was an essential step to address a subset of low-risk thyroid neoplasms that are overtreated. Acceptance of NIFTP as a non-malignant lesion will spare patients from the psychological impact being diagnosed with a "malignancy" as well as additional surgical and clinical treatment and follow-up. The emerging literature indicates that the adoption of strict inclusion and exclusion criteria is essential to correctly diagnose NIFTP. This has led to a revision of the morphological criteria and is a testimony to the fact that embracing NIFTP as a new entity is only the first step toward a more evidence-based approach to managing thyroid neoplasms (Fig. 2). Despite the fact that NIFTP is currently based on a histological diagnosis, we await reliable criteria that might lead to a diagnosis of NIFTP on cytological specimens [53].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

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