Surgical and Experimental Pathology

RESEARCH

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Bethesda Category III thyroid nodules: descriptive cytological aspects of a series

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Abstract

Background *The Bethesda System for Reporting Thyroid Cytopathology* (TBSRTC) is used for cytopathological diagnosis of fine needle aspiration (FNA) of thyroid nodules (TN). Diagnosis of Bethesda Category III (CIII) has estimated malignancy rates of around 10%-30%, which vary between different institutions. Objective. To review cases of FNA interpreted as CIII thyroid nodules. To evaluate cytopathological criteria used to interpret FNA for CIII thyroid nodules and the associations between cytological and radiological aspects. To determine the malignancy rate of thyroid nodules classified as CIII, based on the correlation with surgical procedure. Methods. Retrospective study of FNA's cytologic criteria of TN classified as CIII, carried out between 2010 and 2016. The patients included in the study were those who underwent the first FNA in the service and who were diagnosed with CIII. The patients had their cytological slides and medical records reviewed to detect the conduct flow followed after the CIII diagnosis. All cases that had histological slides available of their thyroidectomy products, total or partial, reviewed. The associations between clinical, histological and cytological findings were statistically studied. Results. Among 63 patients with resected nodules, 17 (27%) were malignant, 13 of which were papillary thyroid carcinomas. Among the benign cases, 18 patients (28.1%) had chronic lymphocytic thyroiditis/Hashimoto's thyroiditis. Papillae ($p = .004$) was the criterion best associated with the diagnosis of malignancy. Conclusion. The malignancy rate was consistent with the rate of malignancy predicted in the TBSRTC. It is important to point out that the sample of this study is relatively small, which compromises specific evaluations and reduces the robustness of the observed data. CIII is extensively studied in the literature, however there is still a need for more precise studies regarding the correlations between cytological findings and other parameters. Probably, more than other categories, CIII may require a combination of cytological, radiological and clinical interpretation, with pathology leading role in this diagnosis process.

Keywords Thyroid gland, Neoplasms of the thyroid gland, Needle biopsy, Cytology, Pathology

Background

Fine needle aspiration (FNA) is the best procedure for assessing thyroid nodules (TN) due to its reliability when combined with ultrasound. In addition, it has a low risk of complications and excellent cost-effectiveness. Previously, the malignancy rate (MR) of surgically resected TN was 14% (Naz et al. 2014; Cibas and Ali 2009a, 2009b). The use of FNA and the establishment of *The Bethesda System for Reporting Thyroid Cytopathology* (TBSRTC) has enabled a more precise diagnosis, resulting in an MR for surgically resected TN of 50%

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(Naz et al. 2014; Cibas and Ali 2009a, 2009b; Ali and Cibas 2010, 2017).

Bethesda Category III (CIII) is the subject of great discussion among medical specialties and is attributed to cases with architectural or nuclear atypia, in which there is no clear evidence of benignity or malignancy. In 2010, the estimated MR for CIII was 5% to 15%. However, interinstitutional variations and recently published studies from different diagnostic centers worldwide have shown a higher MR for CIII than initially expected, ranging from 13% to 36.2% (Ali and Cibas 2010, 2017; Vuong et al. 2020; Bongiovanni et al. 2021; Pusztaszeri et al. 2016; Renshaw 2011; Song et al. 2012; Chen et al. 2012; Nagarkatti et al. 2013; Orlén et al. 2014; Ho et al. 2014; Iskandar et al. 2014; Rosario 2014; Topaloglu et al.2016; Kim et al. 2016). The second edition of the TBSRTC for reporting thyroid cytopathology (2017) reviewed cytomorphological criteria, MR, and included the changes associated with non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The estimated MR has been updated to 10% to 30%. However, considering that the new NIFTP does not fall within the malignant thyroid neoplasms and that it corresponds to a substantial proportion of cases hidden in CIII, the MR will fall to 6% to 18% (Pusztaszeri et al. 2016; Renshaw 2011). CIII is a complex category that combines different TN morphological characteristics. This study reviewed the FNA of TN previously categorized as CIII, seeking cytological characterization to map the radiological and clinical-surgical treatment.

Methods

This is a retrospective cross-sectional study of patients who underwent FNA for TN at the Department of Pathology, Botucatu School of Medicine (FMB UNESP), between 2010 and 2016. The patients were followed by Endocrinology group of the Department of Internal Medicine of FMB UNESP. This study was approved by the local Research Ethics Committee (CAAE: 65.915.917.9.0000.5411).

The inclusion criteria for this study were: patients undergoing FNA with a diagnosis of CIII in their first cytological examination. The patients were studied based on this diagnosis, seeking to understand the new subsequent punctures, the clinical conducts or even the surgical indication. The study only included patients diagnosed with CIII, who had cytopathological slides and those who underwent surgical resection and had histopathological slides, filed at the Department of Pathology at FMB UNESP, with registered clinical follow-up.

Study scenario

FNA of TN at FMB UNESP is performed by the pathologists together with the radiology group. The procedure consists of inserting a fine needle (22G) to aspirate the nodule contents. Smears are performed and stained using two stains for each procedure. One of the stains is Giemsa and second may be Hematoxylin–eosin or Papanicolaou stain. Generally, 5 to 8 slides are performed, which are divided between the two stains. Whenever possible, cell-block is attempted.

Cytopathological evaluation and histological correlation

The pathologists involved in this study reviewed the FNA, which had a CIII diagnosis, seeking to identify the following characteristics, according to TBSRTC (Cibas and Ali 2009a, 2009b; Ali and Cibas 2010, 2017): cellularity of the smear of the lesion, cellular overlap, colloid scarcity (Fig. 1a), imbalance in the cellularity/colloid relationship (Fig. 1b), predominance of macrofollicles (Fig. 1c), presence of overlap similar to three-dimensional blocks (Fig. 1d), predominance of microfollicles (Fig. 1e), nuclear grooves (Fig. 1f), evident nucleoli, clear chromatin (Fig. 1g), pseudoinclusions (Fig. 1h), lymphocytosis (Fig. 1i), plasmocytosis, papillae (Fig. 1 j, k and l), cell/nuclear monotony characterized by uniformity between the elements (Fig. 1m and n), signs of cystic degeneration such as the presence of macrophages, presence of flame cells, multinucleated giant cells, calcifications and the presence of Hürthle cells (Fig. 1o).

The surgical products were reviewed for cases that had thyroid resection to classify them as benign or malignant, in addition to specifying the subtype of lesion. The researchers/pathologists sought to be sure that the nodules studied in the aspiration punctures were the same nodules evaluated in the surgical resections and/or subsequent aspiration punctures.

Review of medical records

The clinical history of each patient was reviewed, seeking the following information: report of radiological examination, repeated FNA, surgical intervention and/or clinical follow-up. If the patient underwent surgical intervention on the TN, the histological slides of the resulting specimen were reassessed. The anatomopathological, cytopathological, and ultrasound reports were reviewed for a careful correlation of the topography and size of the nodule studied.

The medical records were reviewed to collect information such as sex, age at diagnosis, laboratory profile of thyroid hormones, diagnosis of thyroid diseases, such as Hashimoto's thyroiditis and Graves disease, and outcome, for example death, no follow-up, metastatic disease, and

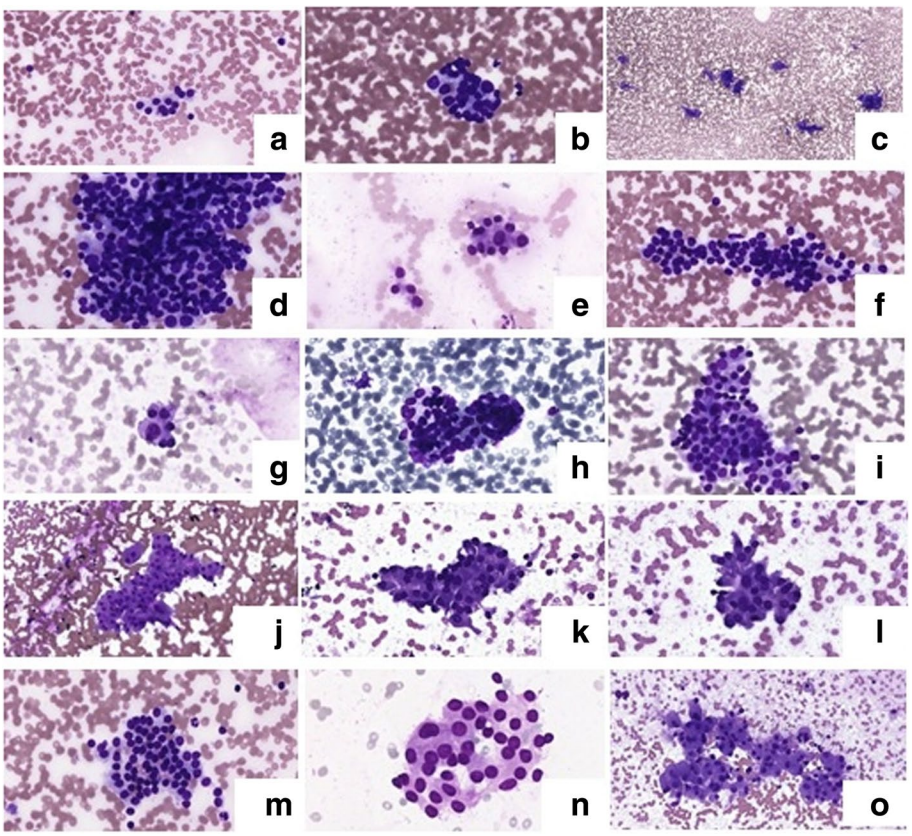

Fig. 1 Cytological findings obtained by FNA of TN, in this study (Giemsa, 400x). **a** colloid scarcity. **b** imbalance in the cellularity/colloid ratio. **c** predominance of macrofollicles. **d** presence of densely cellular macrofollicles with overlap similar to three-dimensional blocks. **e** predominance of microfollicles. **f** nuclear grooves. **g** clear chromatin. **h** and **i** pseudoinclusions (arrows). **i** lymphocytosis (lymphocytes permeating follicular cells—circles). **j**, **k** and **l** papillae. **m** and **n** cell/nuclear monotony characterized by uniformity between the elements. **o** presence of Hürthle cells

cancer treatments. Radiological reports were reviewed, seeking information regarding the nodules, such as: size poor delimitation, hypervascularization, hypoechogenicity, and microcalcifications.

Statistical evaluation

For statistical evaluation, we used descriptive evaluation of cytomorphological, clinical, and radiological data. Quantitative variables were tabulated and analyzed per percentage. The comparisons between the frequencies of the variables were performed with parametric and non-parametric tests, when appropriate, with p-values considered significant when less than 0.05. SPSS software (version 22.0) was used for all calculations.

Results

The casuistic was made up of 73 patients diagnosed with CIII, aged between 10 and 76 years (median 55 years), 7 men (9.6%) and 66 women (90.4%).

After the diagnose, 14 patients (14/73; 19.1%) were underwent repeated FNA and were reclassified as follows: 10 patients as category II (CII – 10/14; 71.4%), 1 patient as category IV (CIV – 01/14; 7.1%), and 3 patients as category V (CV – 03/14; 21.4%). The four patients who were submitted to a new FNA and were reclassified as CV and CIV underwent total thyroidectomy (TT) with a final diagnosis of classic papillary carcinoma (CPC) in 2 patients, follicular carcinoma (FC) in one patient and a nodular goiter/multinodular goiter (NGMG) in one patient. On the other hand, after CIII diagnose, 59 patients were recommended directly for surgical intervention as the initial treatment.

Among the 73 patients of the casuistic, 63 (86.3%) had nodules surgically resected with slides and blocks available for review. In 39 patients, the surgery was partial lobectomy (39/63; 61.9%) and in 24 patients the surgery was total thyroidectomy (24/63; 38.1%). In 17 patients, the final histological diagnosis was malignant (17/63; 27%) and in 46, the histological diagnosis was benign (46/63; 73%). The MR of this casuistic was 26.9% (17/63). Of the malignancies, CPC was the main diagnose and were found in 13 patients (20.6%). Among the benign

Table 1 Proportion of final histopathological diagnoses in 63 patients who underwent surgical resection after FNA with CIII in cytological classification

Diagnosis	CPC	FVPC	SVPC	FC	FA	HCA	NG/MNG	CLT/HT	Total
%	20,6	1,6	1,6	3,2	7,9	1,6	34,9	28,6	100
Number of cases	13	1	1	2	5	1	22	18	63

CPC Classic papillary carcinoma, *FVPC* Follicular variant papillary carcinoma, *SVPV* Solid variant papillary carcinoma, *FC* Follicular carcinoma, *FA* Follicular adenoma, *HCA* Hürthle cell adenoma, *NG/MNG*: Nodular goiter/multinodular goiter, *CLT/HT* Chronic lymphocytic thyroiditis/Hashimoto's thyroiditis

Table 2 Procedures performed and malignancy rate of 73 patients with thyroid nodules classified as category III by the TBSRTC.*

Repetition of FNA 14 cases (19.1%)	**Category II 10 cases**	**Clinical follow-up 10 cases**	**Benign 10 cases (13.7%)**
	Category IV 1 case	**Surgical resection 4 cases**	**Benign 1 case (1.3%)**
	Category V 3 cases		**Malignant 3 cases (4.1%)**
Initial surgical resection 59 cases (80.8%)			**Benign** 45 cases (61.6%)
			Malignant 14 cases (19.2%)

thyroid diseases, NGMG (22/63; 34.9%) and CLT/TH (18/63; 28,6%) were the most frequently conditions. Table 1 describes the specification and proportion of the different entities found Table 2.

The frequency of each cytological finding observed in the 63 patients, with CIII diagnose in the FNA, who underwent surgical resection, is shown in Table 3. In this study, only the presence of papillae, with p-value of 0.004, was the main cytological criterion, with the greatest statistical relevance for malignant cases.

Regard the ultrasound characteristics observed, among the malignant cases in this study, nine patients (56.2%, in relation to malignant cases with ultrasound records) were isoecogenic or hyperechogenic and seven patients (43.8%) were hypoechoic (Table 4).

Discussion

It is protocol that patients diagnosed with CIII nodules undergo a new aspiration puncture. In our casuistic, 14 (19.1%) underwent repeat FNA and were reclassified. The quality of the material in the smears and the presence of artifacts may make the cytopathological analysis difficult (Renshaw 2011). These factors may influence the diagnosis of some cases of CIII. A study by Song et al. (2012) (Song et al. 2012) showed that the presence of atypical follicular cells with preparation artifacts was found in 58.9% of CIII cases that underwent resection. The second edition of TBS states that, in the presence of artifacts of

Table 3 Incidence of cytological findings in cases classified as CIII by the TBSRTC in relation to the final histological diagnosis

Cytological characterization	Malignant ($n = 17$)*	*p*-valor**
Hypercellularity	11 (64.7%)	.337
Overlap	11 (64.7%)	.597
Scarce colloid	12 (70.6%)	.403
Cellularity/colloid imbalance	14 (82.4%)	.544
Solid blocks***	9 (52.9%)	.329
Presence of macrofollicles	15 (88.2%)	.519
Predominance of microfollicles	6 (35.3%)	.447
Focal Hürthle	5 (29.4%)	.153
Difuse Hürthle	4 (23.5%)	.259
Grooves	11 (64.7%)	.468
Nucleolus	14 (82.4%)	.052
Clear chromatin	1 (5.9%)	.302
Papillae	6 (35.3%)	.004
Focal pseudoinclusion	4 (23.5%)	.489
Lymphocytosis	4 (23.5%)	.244
Plasmacytosis	1 (5.9%)	.385
Monotony	9 (52.9%)	.135
Non-psammomatous calcification	0	.73
Cystic	1 (5.9%)	.385
Presence of flame cells	0	.274
Giant cells	4 (23.5%)	.489

In relation to a total of 63 operated patients, 17 patients had histological diagnose of malignant neoplasm. ** Test used: Chi−Square and Fisher's Exact, when appropriate, $p = .05$. * Solid blocks are references to larger macrofollicles, with exuberant cell overlap, sometimes with three−dimensional arrangements, and precise delimitation

Table 4 Association between sonographic characteristics and histopathological diagnosis of malignancy.*

		Malignant ($n = 16$)*	Total cases	*p*-valor**
Echogenicity	**Hypoechogenic**	7 (43.7%)	26	.558
	Isoechogenic	6 (37.5%)	20	
	Hyperechogenic	3 (18.7%)	17	
Doppler vascular flow	**Central flow**	1 (6.2%)	4	.694
	Peripheral flow	5 (31.2%)	23	
	Mixed flow	5 (31.2%)	16	
	No flow	5 (31.2%)	22	
Microcalcifications	**Present**	1 (6.2%)	6	.193
Node margins	**Poorly defined margins**	7 (43.7%)	14	.228

*One classic papillary carcinoma had no ultrasound data in the medical record. ** Chi–square or Fisher's exact test when appropriate, $p < .05$

drying and excessive focal coagulation, but in a benign cytological context, the sample must be classified as CII. If extensive, preventing compliance with standard suitability criteria for well-preserved follicular cells, it should be classified as CI. Only rare cases uncertain as to the nature of atypia, whether artifactual or true, should be classified as CIII (Pusztaszeri et al. 2016).

A study by Higuchi et al. (2018) (Higuchi et al. 2018) also showed the effectiveness of repeated FNA for nodules initially classified as CIII (Higuchi et al. 2018). In their study, among the 15 cases submitted to repeat FNA, 6 were reclassified as CII (40%), 6 continued as CIII (40%) and 3 as CVI (20%). Thus, 60% could be classified as benign or malignant, after repetition of FNA, which helps in the decision regarding the choice for clinical or surgical treatment and may reduce the morbidity related to surgery for benign cases. Nagarkatti et al. (2013) (Nagarkatti et al. 2013) evaluated 203 NT CIII cases and 51 patients underwent repeated FNA. Of these, 17 continued with the classification CIII, while 6 CI, 22 CII, 3 CIV, and 3 CV. Thus, at least 43% of cases could avoid unnecessary surgery based on cytological criteria (Nagarkatti et al. 2013). As reported by these authors, the second FNA seems to result more in benign conclusions, which would have an impact on reducing the surgical morbidity of cervical interventions.

Surgery was recommended as the initial treatment for 86% of the patients. Among the reasons justifying the option for TT is the association with hypothyroidism, correction of symptoms, patient's personal desire and presence of multiple nodules or high clinical suspicion for malignancy (James et al. 2019; Kapan et al. 2015).

In our study, the MR for TN classified as CIII submitted to surgical resection was 27% (17/63). The value is higher than the MR estimated in the first edition of TBS—5% to 15%, but in agreement with the second edition – (10% to 30%) (Bongiovanni et al. 2021). Iskandar et al. (2014) (Iskandar et al. 2014) state that the high rates published could be overestimated because they were carried out in institutions focused on high complexity care. The inclusion of cases of incidental carcinomas, publication bias and interobserver diagnostic variability are other aspects that could justify greater MR. A study by Rosario et al. (2014) (Rosario 2014) emphasizes that the association of cytological findings with ultrasound patterns increase the MR of this classification and can be used in clinical practice to establish treatment plans, according to the institution (Rosario 2014).

Thus, the risk of malignancy in each of the six diagnostic categories should ideally be defined independently in each institution, considering the diagnostic proportions, correlation between clinical and radiological aspects and the geographical reality of the region. Guidance to physicians on malignancy risk estimates helps to define the clinical-surgical approach and indicate appropriate molecular tests for patients that were diagnosed without using the cytological technique (Haugen et al. 2016; Heller 2014).

Only one malignant case had microcalcifications (6.2%) and nine had poorly defined margins (56.2%). Some authors argue that hypoechogenicity, irregular margin and microcalcifications, are the ultrasound findings most related to malignancy, present alone or simultaneously. The interpretation of the nodule margin is the criterion with the highest interobserver variability in the ultrasound assessment of TN. However, the use of high-resolution probes reduces the variability interobserver (Feroci et al. 2023; Russ et al. 2011; Kwak et al. 2011; Ha et al. 2019; Tessler et al. 2017; Wu et al. 2019; Gao et al. 2019; Anil et al. 2011; Wienke et al. 2003). It is necessary to mention the TIRADS classification, a radiological classification that uses sonographic data to group thyroid nodules according to their atypia and risk of malignancy. While classification is important and widely used, not all services adopt it. In the

service of origin of this series, the TIRADS classification is not adopted.

Conclusion

Our results demonstrate a malignancy rate within the literature range. Our research details the cytological criteria that deserve to be evaluated in each smear in order to make a more accurate class diagnosis. Although radiological findings are important, our research was not able to trace a correlation between cytopathology and ultrasound for more accurate classifications. Regardless of the limiting factors, we observed that the presence of papilla is an important finding related to malignancy. Perhaps, in larger samples, more specific correlations can be found, in the sense of Bethesda category III subdivisions.

Abbreviations

FNA	Fine needle aspiration
TN	Thyroid nodules
MR	Malignancy rate
TBS	Bethesda System
NIFTP	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
CPC	Classic papillary carcinoma
BN/BMN	Nodular goiter/multinodular goiter
TT	Thyroidectomy
LT	Lobectomy
GD	Graves disease
HT	Hashimoto's thyroiditis
ETE	Evidence of extrathyroidal extension
ATA	American Thyroid Association

Acknowledgements

The authors thank the Department of Pathology and the Endocrinology team of Botucatu School of Medicine, São Paulo State University (FMB UNESP).

Authors' contributions

JTQR, RGK, MAEM and CCO reviewed pathological slides and diagnosis. RGK, JVT and GMFDSM were responsible for clinical and surgical data. JTQR and CCO were responsible for data analysis and they wrote the manuscript version. All authors reviewed approved the final version of the text.

Funding

This paper did not receive support of financial agencies.

Availability of data and materials

Data may be asked to the author by email address.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee (CEP) (CAAE: 65915917.9.0000.5411) of Botucatu School of Medicine, São Paulo State University (FMB UNESP). Consent to participate obeyed the committee's rules.

Consent for publication

All the authors approved the final version of this research and consented to publication.

Competing interests

The authors do not have any conflict of interest.

Received: 19 April 2023 Accepted: 9 October 2023
Published online: 20 November 2023

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