Hypothesis
Volume 12:3, 2021

Journal of
Cytology & Histology

ISSN: 2157-7099 Open Access

Thyroid Oncocytic Cell in Cytological and Histologic Reports: Institutional Experience

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Abstract

Purpose: Oncocytic cell tumors, due to historical and clinical reasons, tend to be put in a higher risk category compared with other cell type tumors. We tried to define the malignancy risk for this entity.

Methods: At our institution, we studied the risk of malignancy associated with a cohort of 107 thyroid nodules aspirates containing oncocytic cells in the cytology report and we have further analyzed other clinical factors.

Results: A tendency for higher risk of malignancy in male sex was found (31.3% vs. 15.4% in women), the difference, however, was not statistically significant (P = 0.291). Total thyroidectomy was the preferred surgical approach and only 10.3% of patients were submitted to lobectomy. Histopathology reports documented 46.7% hyperplastic/adenomatoid nodules, 31.8% adenomas, 12.1% papillary carcinoma, 3.7% oncocytic cell carcinoma, 2.8% lymphocytic thyroiditis and 1.9% poorly differentiated carcinoma. Benign nodules (Bethesda Class II) exhibited a 9.7% malignancy risk; Class III exhibited a 20% malignancy risk; Class IV exhibited a 18.4% malignancy; Class V exhibited a 16% malignancy risk and Class VI exhibited a 100% malignancy risk. Overall histologic data from the aspirated nodules showed a risk of malignancy of 17.8%.

Conclusion: Our study seems to suggest that in the presence of oncocytic cells there may be a tendency for a higher than expected malignancy rate. Clinical factors appear to be insufficient to base our management decisions with confidence and molecular markers are still under development. Therefore, surgery may stand as the favored option in this setting.

Keywords: Hürthle Cell • Oncocytic Cells • Oxyphil Cells • Cytology

Introduction

In order to address thyroid nodules - which can be present on physical examination in 5% of women, 1% of men and more frequently on ultrasound (19-68%) - fine-needle aspiration cytology (FNAC), the gold standard for their evaluation, is of paramount importance to identify clinical relevance and hence surgical indication [1,2].

One of its main limitations, discerning benign neoplasms from malign, is particularly relevant albeit controversial when considering Hürthle-Askanazy cells [3,4].

Oncocytic or oxyphil cells (the preferred terms according to WHO) are metaplastic cells that do not correspond to any specific pathological process [5]. Their cytomorphologic features include large round to oval hyperchromatic nuclei with prominent nucleoli and a voluminous, granular, eosinophilic cytoplasm, enclosing a large quantity of mitochondria, usually displaying a low nuclear-cytoplasm ratio. They can be found in multiple other tissues, such as kidney, adrenal cortex, parathyroid, pituitary gland and pancreatic islets e.g. Thyroidal pathologies containing oncocytic cells are usually found in older patients and range from benign hyperplastic nodules associated with long-established Hashimoto's thyroiditis, Graves disease and multinodular goiters, to adenomas, and ultimately, malign oncocytic cell carcinomas [6-10].

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Received 24 February 2021; **Accepted** 10 March 2021; **Published** 17 March 2021

According to Bethesda System, the presence of a small population of oncocytic cells does not grant the classification of "Follicular neoplasm" or "Suspicious for a follicular neoplasm". The cytologic and histologic definition of oncocytic cell tumor requires a predominance of this cell type and ideally follows the >75% criterion for both the aspirate and the histologic specimen [8,11].

Classically, these tumors have been thought to carry a higher carcinoma risk when compared to its equivalents, as well as a less favorable prognosis [12,13]. The fourth edition of *WHO: Classification of* Tumours of Endocrine Organs defines these tumors as a separate entity and highlights one of its main clinically relevant differences: their radio-iodine resistance, which could account for differences in prognosis [8]. However, these have been contested and similar prognoses have also been described [14, 15].

As mentioned before, FNAC cannot fully differentiate between benign and malign lesions in this setting and, as of now, there is no available pre or intra-operative technique to enable this differentiation [16]. Even distinguishing between hyperplasia and neoplasm is problematic [17]. Increased oncocytic and global cellularity and the absence of colloid were the only cytomorphologic features that could be associated with neoplastic lesions and no feature could exclude them [18]. All in all, because only capsular or vascular invasion will determine the classification as carcinoma, surgery is usually offered to the majority of patients, in the form of a lobectomy or total thyroidectomy [19]. Approximately, one third of these patients will have a benign non-neoplastic lesion, one third will have an adenoma and the other third will have a malignant tumor [11,20].

Nevertheless, an effort was made in recent years to find criteria or techniques to help pathologists distinguish between benign and malign cases. Some known clinical factors correlated, although inconsistently, with higher malignant outcomes on histology: tumor size, elderliness and male sex [20, 21].

Interestingly, some defend that while it is not always possible to distinguish

oncocytic cell carcinomas from adenomas using FNAC, it can be possible to discriminate some non-malign lesions as clearly benign, which could potentially alleviate unnecessary burden for patients, clinicians and lastly health services [22,23]. Moreover, in the future we might have biomarkers and immunohistochemical methods supporting this endeavor. D-type cyclins (D1 and specially D3), p53, MIB1, Ki67, Bcl-2, microRNA analysis are some of the potential candidates [24].

When active surveillance approach is not an option, which is frequently the case for oncocytic tumors, lobectomy would be the usual surgical option. However, total thyroidectomy may be the choice: if there is a previous history of relevant irradiation; in patients with contralateral nodules; or if after informing the patients about the additional risk of complications after a more aggressive procedure, they express apprehension about malignancy or wish to avoid additional surgery [25].

Since distinction between different cytologic diagnostic categories is particularly challenging when oncocytic cells are present, we decided to study the rate of malignancy in a population of patients' histologic specimens from our institution, in which FNAC had been positive for oncocytic cells. In addition, we sought to highlight eventually associated clinical nuances concerning malignancy risk.

Materials and Methods

We scrutinized retrospectively all FNAC reports generated from the 1st of January 2012 to the 30th of April 2018, at Hospital of Santa Maria in Lisbon, using the keywords "Oncocytic" and "Hürthle" for search purposes. From 325 FNAC reports found, we selected the patients that were submitted to surgery and subsequently, histology was available.

A pathologist performed the majority of aspirations, the main exception being when the nodule was not palpable, in which case a radiologist executed an ultrasound-guided FNAC. Evaluation of the cytologic specimen was done by the cytopathologist.

The following clinical data was collected using the hospital information system: age, sex, laterality of the nodule and surgical procedure. Size of the nodule was acquired by ultrasound data or macroscopic evaluation of the histologic specimen. The remaining information resulted from cytology/histology reports, namely, malignancy of the aspirated nodule and incidentally found malignant lesions.

Statistical exploration of pathological and clinical parameters was achieved using IBM's Statistical Package for the Social Sciences (SPSS) version 25. A P value <0.05 was considered significant.

Results

Our study cohort was composed of 107 patients, with an age range between 19 and 94 years and a mean of 60 years. 91 patients were female. Mean age for benign outcome on histology was 62 years and for malignant outcome 53 years (P=0.027). When age was grouped, a malignant outcome was present in 9 of 39 patients <55 years (23.1%) and 10 of 68 patients ≥ 55 years (14.7%) – this was not statistically significant (P=0.214).

Within female sex, there was a malignant diagnosis in 14 of 91 cases (15.4%) vs. male sex 5 of 16 (31.3%). Although statistical significance was not achieved there was a tendency for higher risk of malignancy in male sex (P=0.291).

The size of the aspirated nodule, and therefore, the one containing oncocytic cells, ranged from 0.7 to 8.0 cm, with a mean of 2.9 cm. 22.6% of nodules were <2 cm, 53.8% were ≥ 2 cm and < 4 cm, 23.6% were ≥ 4 cm. Mean age for nodules <2 cm was 57 years and for nodules ≥ 2cm was 62 years (P = 0.13).

Aspirated nodules ≥ 4 cm had a slightly lower risk of malignancy than the <4 cm group (16.0% vs. 18.5%), although not statistically significant (P=0.466).

Cytology reports presented a Bethesda Class II (benign) outcome in 31 cases (29.0%), Bethesda Class III (follicular lesion of undetermined significance – FLUS) in 30 cases (28.0%), Bethesda Class IV (follicular neoplasm) in 38 cases (35.5%); Bethesda Class V (suspicious for malignancy) in 6 cases (5.6%) and Bethesda Class VI (malignant) in 2 cases (1,9%).

43.9% of the nodules aspirated were located in the right lobe, 48.6% on the left lobe and 7.5% were isthmic.

A lobectomy was performed in 11 cases (10.3%) and in 96 cases total thyroidectomy was the chosen option (89.7%).

From those 11 lobectomy cases, 3 had a benign cytology, 6 were FLUS and 2 were classified as follicular neoplasm. None of the aspirates previously classified as benign (Class II) revealed malignancy in histology analysis; 2 FLUS revealed papillary carcinomas; 1 follicular neoplasm revealed an oncocytic cell adenoma.

Overall histologic analysis of the aspirated nodules documented 50 hyperplastic/adenomatoid cases (46.7%), 34 adenomas (31.8%), 13 cases of papillary carcinoma (12.1%), 4 cases of oncocytic cell carcinoma (3.7%), 3 cases of lymphocytic thyroiditis (2.8%), 2 cases of poorly differentiated carcinoma (1.9%), and 1 case of follicular tumor of uncertain malignant potential (0.9%).

Oncocytic cells were described in histology report in 78 cases and in 29 cases its existence was not mentioned. 24 of 29 of these cases corresponded to benign histologic outcomes, 5 were papillary carcinomas (2 of them had malignant FNAC reports, 2 were FLUS and 1 was benign), 3 cases corresponded to adenomas. In 2 cases an incidental carcinoma was found.

Histologic analysis of the aspirated nodule in females documented 11 papillary carcinoma (12.1%), 2 oncocytic cell carcinoma (2.2%) and 1 poorly differentiated carcinoma (1.1%) ~ 15% malignancy. Histologic analysis of the aspirated nodule in males documented 2 papillary carcinoma (12.5%), 2 oncocytic cell carcinoma (12.5%), 1 poorly differentiated carcinoma (6.3%) ~ 31% malignancy.

Oncocytic cell carcinoma and poorly differentiated carcinoma were more prevalent in the ≥ 4 cm nodules group (8.0% vs. 2.5% and 4.0% vs. 1.0%, respectively), but papillary carcinoma was more prevalent in the <4 cm group (15.0% vs. 4.0%). Adenomas and hyperplastic/adenomatoid nodules had similar percentage of cases in both groups (32.0% and 46.0%, respectively). 1 case of follicular tumor of uncertain malignant potential was found in the ≥ 4 cm group.

Regarding the aspirated nodules description in histology report:

- Among benign nodules, according to Bethesda classification, hyperplastic/adenomatoid result was the most frequent with 23 of 31 cases, followed by 3 adenomas, 3 papillary carcinoma and 2 cases of lymphocytic thyroiditis – 9.7% malignant outcome.
- Among aspirated nodules classified as *FLUS*, 14 of 30 cases of hyperplastic/adenomatoid nodules were found, 10 cases of adenoma, 5 cases of papillary carcinoma and 1 oncocytic cell carcinoma – 20.0% malignant outcome.
- Among follicular neoplasm, adenomas were the most frequent finding with 19 of 38 cases, followed by hyperplastic/adenomatoid nodules with 11 cases, oncocytic carcinoma with 3 cases, 2 cases of poorly differentiated carcinoma, 2 papillary carcinoma and 1 follicular tumor of uncertain malignant potential – 18.4% malignant outcome.
- Among suspicious for malignancy there were 2 cases of hyperplastic/adenomatoid nodule, 2 cases of adenoma, 1 case of papillary carcinoma and 1 case of lymphocytic thyroiditis – 16% of malignant outcome.
- 2 malignant nodules in cytology corresponded to 2 papillary carcinomas in histology.

The final histologic diagnosis was benign in 87 cases (81.3%) and malignant in 19 (17.8%), one case was uncertain for malignancy.

Incidentally found carcinomas were present in 16 cases (15.0%), 12 papillary microcarcinomas, 3 papillary carcinomas (1 multifocal) and 1 medullary carcinoma.

Discussion

Nowadays, FNAC has become a standard of care for thyroid nodular disease. Not unexpectedly, shortcomings related to its extensive use may ensue.

Sensitivity is often considered as more important than specificity, as diagnosing a potentially malignant lesion secures more importance than carefully weighting the gains and risks associated with an impending surgical procedure. This reality is even more pertinent when considering oncocytic cell lesions, on the one hand due to historical increased concern regarding its behavior and on the other hand due to its challenging cytopathologic features.

In our institution, we follow Bethesda System for reporting thyroid cytopathology and, as such, the mere presence of oncocytic cells did not grant the classification as follicular neoplasm. Nonetheless, 31 patients whose aspirated nodules classified as benign (and positive for oncocytic cells) were submitted to surgery, which can be explained by the presence of large goiters, with compressive symptoms and by clinical evolution suggestive of higher risk of malignancy, eventually not detected with FNAC.

Total thyroidectomy was largely the predominant choice, and that remained true for Class II and III, mostly due to the existence of contralateral nodules and/or patient anxiety.

Comparing with data from the literature, which pointed to a one third “rule” distribution we found 17.8% of malignancy in aspirated specimens, 31.8% adenomas and 49.5% non-neoplastic lesions. As mentioned before, 1 case of follicular tumor of uncertain malignant potential was documented.

If we would include incidentally found carcinomas in the final score for malignancy we would get 32.7% malignant outcome.

In our study, age could not be associated with higher risk of malignancy. In actual fact, mean age for malignant outcome was lower. This can be explained by submission to surgery unrelated to cytology findings in large multinodular goiters belonging to older patients, some with long lasting Hashimoto’s thyroiditis, whereas a younger patient submitted to surgery usually signified clinical suspicion was higher.

Size of nodule related poorly with overall malignancy in our data. However, oncocytic cell carcinoma was more prevalent in nodules ≥ 4 cm.

The most consistent clinical factor related to higher malignancy was male sex (P=0.291). 31.3% of male patients had a malignant tumor in histologic report.

In 19 malignant cases only 1 case had metastatic ganglia (a multifocal papillary carcinoma with a concomitant oncocytic cell adenoma), and no case had distant metastasis. Incidentally found carcinomas were present in 15.0% of cases which is similar to other described series [26,27]

When we matched our results with what is described in Bethesda System [11] for risk of malignancy, we found:

- Class II (benign) exhibited a 9.7% malignancy risk (vs. 0-3% according to Bethesda System)
- Class III (FLUS) exhibited a 20% malignancy risk (vs. 10-30%)
- Class IV (follicular neoplasm) exhibited a 18.4% malignancy risk (vs. 25-40%)
- Class V (suspicious for malignancy) exhibited a 16% malignancy risk (vs. 50-75%)
- Class VI exhibited a 100% malignancy risk (vs.97-99%)

Although one could discuss the clinical gain (reduced mortality vs. induced morbidity) of diagnosing some of these malignant lesions, it is difficult to overlook the evidence that seems to point towards considering the surgical attitude as the most tranquilizing for both clinicians and patients in the setting of Class III and IV cytological findings.

In 5 Class V cases only 1 malignant outcome was revealed on histological report of the examined nodule. Nonetheless, 2 incidental carcinomas were found (1 papillary and 1 medullary).

Convincing methods for assessment of malignancy risk are lacking. Cytologic criteria can be developed for oncocytic cell tumors but sensitivity will probably retain its predominance. Clinical factors are useful to categorize risk in theory, but will hardly be able to change the course of action in these patients.

In order to overcome the tendency to associate oncocytic cell findings with imminent surgery, given the high percentage of malignancy found in each cytologic class, more advanced molecular techniques will have to be developed.

Acknowledgments

In our institution, we thank the pathologists for their work on the cytological and histological reports, and the surgeons of the endocrine surgery unit for their skilled contribution.

Compliance with Ethical Standards

The authors declare no conflict of interest is present.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

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How to cite this article: José Marçalo MD, Mónica Cardoso MD, Dolores López Presa MD and Maria João Bugalho MD, Ph.D. Thyroid Oncocytic Cell in Cytological and Histologic Reports: Institutional Experience. J Cytol Histol 12 (2021): 560.