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Original Article

Cytomorphologic Spectrum of Hurthle Cell Lesions of Thyroid: A Study of 54 Cases

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Abstract

Introduction: Lesions of the thyroid gland composed of Hurthle cells constitute a wide spectrum of pathological entities ranging from benign hyperplastic nodules with Hurthle cell metaplasia at one end to malignancies like Hurthle cell carcinomas. The cytological distinction of these entities is not only diagnostically challenging but are also critical since they influence treatment decisions.

Aim: To critically analyze the cytomorphology of cases of Hurthle cell lesions in FNACs and to characterize cytological features shown to be statistically significant in predicting Hurthle cell neoplasm (HCN).

Methods: During the period from January 2014 to August 2015, 1667 cases of thyroid FNAs were done at our centre, of which 54 cases showed a predominance of hurthle cells, i.e. more than or equal to 50% hurthle cells (>/=50%). These cases were included in the study and were critically reviewed for 9 cytomorphologic features which included cellularity, architecture, and percentage of Hurthle cells, background colloid, chronic inflammation, nucleoli, intranuclear cytoplasmic inclusions (INCI), nuclear grooves and transgressing blood vessels (TBV). The results were evaluated by using univariate and stepwise logistic regression (SLR) analysis; statistical significance was achieved at P-value < 0.05.

Results: Out of the 9 parameters studied, the cytological features shown to be statistically significant in predicting HCN and distinguishing them from benign hurthle cell lesions (BHCLs) were increased cellularity, non-macro follicular architecture, >90% Hurthle cells, absence of background colloid and absence of chronic inflammation.

Keywords: Hurthle cells, hurthle cell neoplasm, cytology, statistical analysis

Introduction

Thyroid fine-needle aspiration (FNA) is a standard triage procedure in the management of thyroid nodules. The clinical decision-making regarding the treatment of thyroid nodules is heavily influenced by cytological diagnosis along with other parameters like the size of the nodules, radiology and the patient’s age, among other risk factors. Though there were previous studies in the literature regarding clinical factors which could predict malignancy in Hurthle cell neoplasms (HCNs) there was no uniformity in the observations made in these studies.¹,²

Hurthle cells are characterized by abundant, granular, eosinophilic cytoplasm with round nuclei and prominent nucleoli. Such cells are also referred to as oncocytes or oxyphilic cells. Thyroid FNA with a predominance of hurthle cells can be seen in many conditions ranging from benign conditions like metaplastic hurthle cell nodules in nodular colloid goiter, nodules of Hashimoto thyroiditis, Graves’ disease where hurthle cell predominance may be seen in FNA does not require surgical management. To distinguish hurthle cell neoplasm requiring surgical intervention from hurthle cell lesions which can be managed medically can be difficult in cytology. However advanced techniques like immunohistochemistry and molecular studies have also given different outcomes in different studies in diagnosing HCNs and hence their reliability is doubtful.³,⁴

In this study we have attempted to statistically characterize cytomorphological features which may help in distinguishing HCN from the BHCL cases showing a predominance of hurthle cells.
Table 1. Scoring of cytomorphological features

<table>
<thead>
<tr>
<th>Cytological feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellularity</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
</tr>
<tr>
<td><strong>Cytoarchitecture</strong></td>
<td></td>
</tr>
<tr>
<td>Macro follicular</td>
<td>0</td>
</tr>
<tr>
<td>Non-macro follicular</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hurthle cells</strong></td>
<td></td>
</tr>
<tr>
<td>50-90%</td>
<td>1</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>2</td>
</tr>
<tr>
<td><strong>Background colloid</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Scanty</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>Abundant</td>
<td>3</td>
</tr>
<tr>
<td><strong>Chronic inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nucleoli</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td><strong>Intranuclear cytoplasmic inclusions</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nuclear grooves</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td><strong>Transgressing blood vessels</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Univariate – Logistic regression analysis

<table>
<thead>
<tr>
<th>Cytological feature score</th>
<th>Sig.</th>
<th>Odds ratio</th>
<th>95.0 % CI. for Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellularity score 3 vs (2+1)</td>
<td>0.0000</td>
<td>50.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Absent colloid score 0 vs (2+3)</td>
<td>0.0003</td>
<td>98.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Colloid score 1 vs (2+3)</td>
<td>0.3847</td>
<td>2.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Inflammation score 0 vs 1</td>
<td>0.0000</td>
<td>27.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Architecture 0 vs 1</td>
<td>0.0169</td>
<td>13.3</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt;90% hurthle cells score 1 vs 0</td>
<td>0.0000</td>
<td>247.0</td>
<td>20.6</td>
</tr>
<tr>
<td>Nucleoli score 1 vs 0</td>
<td>0.7880</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCl score 1 vs 0</td>
<td>0.7880</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBV score 1 vs 0</td>
<td>0.8224</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING score 1 vs 0</td>
<td>0.2299</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Materials and Methods

During the period from January 2014 to August 2015 a total of 1667 patients were referred to our cytopathology division for FNAC of thyroid. FNA of the thyroid is done using 23 G needle. Both aspiration and non-aspiration technique are used. A maximum of 2 attempts are made to procure material. The smears are fixed in ethanol and stained with papanicolaou stain.

Out of the 1667 cases, 54 cases with a predominance of hurthle cells (>/=50% hurthle cells); were included in the study. These 54 cases were critically reviewed for 9 parameters (Table 1); cellularity (score 1 to 3); architecture (macro follicular architecture present/absent); percentage of hurthle cells (50–90%/ >90%); background colloid (score 0 to 3); chronic inflammation (present/absent); nucleoli (present/absent), nuclear grooves (present/absent); intranuclear cytoplasmic inclusions (present/absent); transgressing blood vessels (present/absent).

The smears were scored depending on their cellularity, a smear of low cellularity was given a score of 1, moderately cellular smears were given a score of 2 and highly cellular smears were given a score of 3. Presence of cohesive, two dimensional cell clusters corresponded to macro follicular architecture, score 0. Micro follicles, single cells, three dimensional cell clusters were grouped into non–macro follicular architecture and given a score of 1.

Depending on the amount of background colloid in smears score of 0 to 3 was given; 0 for absence of colloid and 3 for abundant colloid. (Figure 1A) Chronic inflammation was defined as the presence of lymphocytes in the background, whether singly scattered in the background or florid lymphocytic infiltration. (Figure 1B) In either case score of 1 was given and if no lymphocytes were present score of 0 was given. TBV were defined as fragments of capillaries coursing through loosely cohesive groups or sheets of Hurthle cells. (Figure 1C,1D) Nucleoli, INCl and nuclear grooves depending on whether present or absent were scored as 0 or 1.

Histopathology correlation was done wherever possible in HCN cases. In cases of thyroiditis, Graves’s disease, TFT values including T3, T4, TSH and antithyroid antibody values were correlated. The results of the 9 cytomorphological features were evaluated by using univariate and multivariate logistic regression (MLR) analysis; statistical significance was achieved at P–values < 0.05.
Out of the 54 cases, 15 cases were diagnosed cytologically as HCN. Of these in 6 cases a possibility of carcinoma could be suggested. BHCLs were also diagnosed during this period. BHCL cases included 22 cases of Hashimoto thyroiditis, 14 cases of colloid nodule with hurthle cell change, 3 cases of Graves’ disease.

Histopathology follow up was available for 7 cases of HCN, these included 4 cases of papillary carcinoma, oncocyct variant, 2 cases of hurthle cell carcinoma and 1 case of hurthle cell nodule. Patients with cytological diagnosis of Hashimoto thyroiditis (HT), Graves’ disease the radiology, TFT values, antithyroid antibody values all supported FNA diagnosis. Patients are on follow up at our thyroid clinic.

Cytological evaluation of the 15 cases in the HCN category demonstrated that 93% cases exhibited a non-macrofollicular architectural pattern that included discohesive groups with single cells, microfollicles. However, majority of cases in the BHCL category exhibited a macrofollicular pattern. Follicular cells in both groups had abundant granular oncocyct cytoplasm and round nuclei with distinct nucleoli. Nuclear pleomorphism, nucleolar prominence, nuclear grooves were seen in variable proportions in both the groups and hence these features were of not much help in differentiating HCN from BHCL. Background colloid was a helpful feature in distinguishing HCNs from BHCLs. 95% BHCL cases contained background colloid, whereas only 4 (27%) HCN cases contained colloid. In addition, 13 cases (86%) of HCN showed more than 90% hurthle cells, whereas only one case (2.5%) of BHCL showed more than 90% hurthle cells. Presence of chronic inflammatory cells was a feature associated more with BHCLs, 34 cases (87%) in contrast to 2 cases (13%) among the HCN cases. High

Results

Out of the 54 cases, 15 cases were diagnosed cytologically as HCN. Of these in 6 cases a possibility of carcinoma could be suggested. BHCLs were also diagnosed during this period. BHCL cases included 22 cases of Hashimoto thyroiditis, 14 cases of colloid nodule with hurthle cell change, 3 cases of Graves’ disease.

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cellularity (score 3) was seen in 11 cases (73%) of HCNs. Only 2 cases (5%) of BHCLs showed a high cellularity.

By univariate logistic regression analysis (Table 2), out of the nine cytomorphological features evaluated, five were found to be statistically significant in diagnosing HCN and differentiating them from BHCLs. These 5 features included high cellularity, absence of colloid, absence of inflammation, more than 90% hurthle cells and non-macro follicular architecture. When multivariate logistic regression analysis (Table 3) was applied to analyze these 5 factors which were found to be statistically significant by univariate logistic regression analysis, the most significant factor of statistical significance in diagnosing HCN was found to be the factor more than /equal to 90% hurthle cells.

Discussion

Distinguishing HCNs from BHCLs based on cytomorphology can be challenging. However, this differentiation is clinically crucial since HCNs require surgical intervention and BHCLs in most instances does not require surgery. Misdiagnosis of BHCLs as HCNs can result in unnecessary surgeries. Previous studies have attempted to identify cytomorphological features helpful in diagnosing HCNs from among hurthle cell rich cytological smears. Kini et al had stressed upon monomorphism, macro nucleoli and cytoarchitecture, Another study has highlighted features like intracytoplasmic inclusions (INCI) and transgressing blood vessels (TBV) to be of use in identification of HCNs. However the reliability of these observations is limited since the study was limited by small size of the study group.

In this study we analyzed 9 cytomorphological features and by applying univariate logistic regression analysis, we have identified five statistically significant cytomorphologic features among them that were helpful in distinguishing HCN from BHCL on FNAB. These included high cellularity, non-macro follicular architecture, absence of colloid, absence of chronic inflammation, and presence of 90% hurthle cells. When these 5 features were analyzed by multivariate logistic regression analysis the most statistically significant factor was the presence of ≥ 90% hurthle cells.

Hyperplastic nodules of HT can be easily mistaken for HCN. Establishing the presence of chronic inflammation helps to prevent them from being placed in HCN category. Thyroid FNACs are often admixed with blood, hence it is important to correlate with differential count in peripheral blood picture to confirm chronic inflammation.

The presence of lymphocytes and plasma cells in close association with follicular cells is highly suggestive of chronic inflammation, especially presence of plasma cells. Even minimal chronic inflammation is highly significant in ruling out HCN and hence a thorough examination of the smears for inflammation is mandatory.

Absence of colloid is another factor statistically significant in predicting HCNs. The statistical significance is markedly reduced even when minimal amount of colloid is present (P value 0.0003 to 0.3847). Hence, it is important to screen thoroughly for the presence of even scanty amount of colloid before categorizing cases as HCNs. Absence of colloid is associated with trabecular, solid, or microfollicular morphology, which are all seen in follicular neoplasm as against macro follicular architecture monolayered sheets seen in hyperplastic nodules. Presence of colloid and inflammation is mostly seen in BHCLs.

Every case included in the present study had >50% hurthle cells. However, the criteria of ≥90% hurthle cells was found to be statistically significant in predicting HCN. We have come across occasional cases of HT with around 90% hurthle cells; however, the associated features like chronic inflammation help in correctly placing such cases in the BHCL category.

Non-macrofollicular architecture was one of the statistically significant cytomorphologic features for predicting HCN that was identified in our study (P value 0.02). This feature is helpful in diagnosing follicular neoplasms, including hurthle cell neoplasm and includes micro follicles, three dimensional cell clusters and single cells. In contrast BHCLs have monolayered flat orderly sheets.

Cellularity of smears were scored from 1 to 3 corresponding to low, medium and high cellularity. All HCN cases invariably had high cellularity. Only occasional cases of hyperplastic nodules had high cellularity. HT cases mostly had intermediate cellularity and cellularity was mostly due to lymphocytes than hurthle cells. The failure to evaluate a predominance of Hurthle cells in the context of other cytomorphologic features such as cytoarchitecture can result in the overtreatment of benign conditions. Some of the previous studies have however come to the conclusion that HCN cannot be reliably diagnosed based on cytological features.

<table>
<thead>
<tr>
<th></th>
<th>Sig.</th>
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<td>20.6</td>
</tr>
</tbody>
</table>

Table 3. Multivariate – logistic regression analysis

Hyperplastic nodules of HT can be easily mistaken for HCN. Establishing the presence of chronic inflammation helps to prevent them from being placed in HCN category. Thyroid FNACs are often admixed with blood, hence it is important to correlate with differential count in peripheral blood picture to confirm chronic inflammation.
we are of the opinion that an experienced cytopathologist when provided with the clinical and radiological details can differentiate HCN from BHCL based on cytomorphology in most instances.

One of the more recently described cytomorphologic features used in the evaluation of HCN is TBV. TBV is characterized by intimate association of thin, delicate capillaries with groups of discohesive Hurthle cells. In our study we came across this feature in only one of our case of HCN. In statistical analysis the P value was only 0.8. However, this feature was not observed in any of BHCLs; hence we are of the opinion that its high specificity makes it an important means of distinguishing HCN from BHCL.

Cytomorphologic features related to nucleus such as prominent nucleoli, INCI, nuclear grooves were not found to be statistically significant, which is not unexpected because a wide range of atypia is known to occur in the cells of non–neoplastic as well as neoplastic nodules of the thyroid gland. We have come across Hurthle cells in hyperplastic nodules of HT exhibiting nuclear atypia. In prior studies, ICL was found to be useful in the diagnosis of HCN and in distinguishing them from BHCLs. In our study also we found this feature to have high specificity in diagnosing HCNs. None of the cases of BHCLs in the present study demonstrated this feature. However, this feature was not statistically significant since only 3 of our HCN cases showed this feature. Presence of nuclear grooves is a non–specific feature since some of our BHCL as well as HCN cases shared this feature.

In conclusion, we evaluated 9 cytomorphologic features in a series of 54 Hurthle cell nodules and demonstrated by statistical analysis that 5 of these features were statistically significant for diagnosing HCN: non–macrofollicular architecture, absence of chronic inflammation, absence of background colloid, > 90% Hurthle cells, and high cellularity. Among these 5 features by multivariate logistic regression analysis, the most significant factor was found to be the presence of > 90% Hurthle cells. Because HCL present a particularly challenging component of thyroid pathology, the cornerstone critical to managing hurthle cell nodules is a highly skilled, experienced pathologist. (12)

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