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Hurthle Cells in Thyroid Cytology

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ABSTRACT

Aim: *Fine needle aspiration cytology of the thyroid gland is firmly established as a first line diagnostic test for the evaluation of goiter and the single most effective test for the preoperative diagnosis of a solitary thyroid nodule. Hurthle cells are of uncertain significance in thyroid disease and the aim of this study is to clarify the meaning and predictivity of Hurthle cells in Fine needle aspiration cytology for thyroid nodular disease.* ***Materials and methods:*** *A total of 210 thyroid Fine Needle Aspiration Cytology smears were studied ,out of which 103 smears showed Hurthle cells with varying morphological features. Smears were stained with Haematoxylin and Eosin stain and May Grunwald Giemsa stain. The cytological smears were studied on the basis of cellularity, amount of colloid, macrophages, lymphocytes, plasma cells, percentage of Hurthle cells compared with all follicular cells, percentage of single Hurthle cells ,cellular arrangement, cohesion, nuclear enlargement, nuclear pleomorphism, nucleoli and binucleation or multi nucleation.* ***Results*** *: Hurthle cells in the neoplasm was compared with non neoplastic Hurthle cell lesions. Statistical analysis was performed with Chi-Square test and statistically significant differences were noted. A P value < 0.05 was considered significant.* ***Conclusion:*** *We conclude that Cytological features of Hurthle cells varied in different lesions of the thyroid, which enables us to differentiate between non-neoplastic and neoplastic lesions and could also guide the clinicians regarding further therapeutic management.*

KEYWORDS : Hurthle cells, Hurthle cell lesions, Thyroid cytology.

I. Introduction

Oncocytes also known as Hurthle cells, Oxyphilic cells or Askanazy cells are characterized by abundant granular cytoplasm due to accumulation of mitochondria. This is a phenomenon of metaplasia and indicates degenerated follicular epithelial cells that occurs in inflammatory disorders such as thyroiditis or situations that results in stress. 'Proliferation of oncocytes gives rise to hyperplastic and neoplastic nodules'

There has been renewed interest in the diagnosis and treatment of Hurthle cell lesions because of the increasing use of fine needle aspiration biopsy in the preoperative diagnosis of thyroid nodules. The present study was undertaken to analyse the cytomorphology of Hurthle cells in Fine Needle Aspiration Cytology Smear and their significance in differentiating Hurthle cell tumours and non-neoplastic Hurthle cell lesions.

II. Materials and Methods

IIa. Experimental Design

The present study was under taken in the Department of pathology, Meenakshi Medical College, Tamil Nadu, India for a period of two years from Jan 2013 -December 2015, during which time we studied a total number of 210 thyroid Fine Needle Aspiration Cytology Smears, out of which 103 smears showed Hurthle cells with varying morphological features.

The cytological materials were obtained in the form of smears which were fixed in 95% alcohol for Haematoxylin and Eosin stain and methanol for May Grunwald Giemsa stain. The aspiration syringes used were 5ml and the needle size between 22-23 gauges.

Procedure

The thyroid gland is palpated carefully and the nodule(s) to be biopsied identified. The procedure is explained to the patient carefully and after informed consent the patient is placed supine with the neck hyperextended to expose the thyroid. For support a pillow is placed under the shoulders. The patient is asked not to swallow, talk or move during the procedure. After the aspiration firm pressure is maintained on the biopsy site. The patient is asked to sit for a few minutes. .

Usually 2-3 aspirates and preferably the aspirates should be obtained from the peripheral areas and different parts of the nodule in a sequential manner to ensure representative sampling. For cystic lesions the fluid should be aspirated and fine needle aspiration cytology attempted on residual tissue[1] The smears were stained in Haematoxylin and Eosin Stain[2] and May Grunwald Giemsa Stain. For tissue sections the specimens were fixed in formalin. After paraffin embedding 4 micron thick sections were made and stained with Haematoxylin and Eosin[2].

For assessing cellularity, the rule of thumb of six groups of normal - appearing thyroid epithelial cell, should be well fixed and well stained, appear unremarkable and benign and should not be excessively degenerated. A group is defined as 15 -20 thyroid epithelial cells in a sheet or follicular group. For assessing the adequacy of specimens, degenerative foam cells are not counted because they are encountered in both benign and malignant (especially papillary) conditions.

Table 1. Occurrence of Hurthle Cells[3]

Non-Neoplastic	Neoplastic
1)Chronic Lymphocytic Thyroiditis and variants. 2) In nodular goitre 3)In diffuse toxic goiter 4)Post irradiation 5)Post chemotherapy **6)** As aging process	Follicular, Hurthle cell adenomas and Carcinomas. Rare variants of papillary and medullary Carcinomas.

III. Statistical Analysis

Data were analyzed using the SPSS software package, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed using range, mean, SD, and median, whereas qualitative data were expressed as frequency and percentage. P value was assumed to be statistically significant at 0.05.

IV. ETHICAL CONCERN

Ethical clearance was obtained from the Ethical committee meeting conducted at Meenakshi Medical Collge and Research Institute, Kanchipuram, Tamil Nadu, India

V. RESULTS AND OBSERVATION

Figure - 1: Showing sex incidence

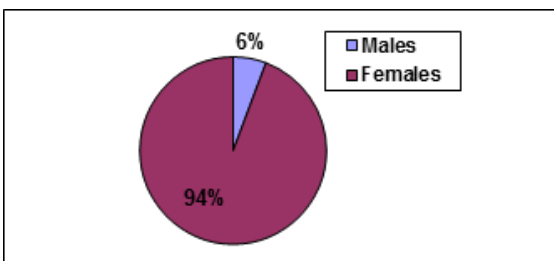
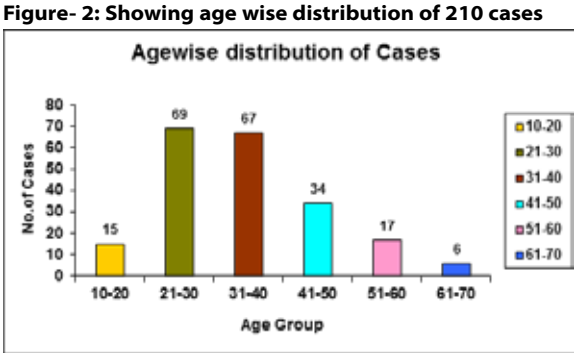


Figure- 2: Showing age wise distribution of 210 cases



In our study of 210 cases of Fine Needle Aspiration of Thyroid, it was found that 103 cases showed a predominance of Hurthle cells .The sex incidence was found to be 12 males and 198 females that is in the ratio of 1:16.5 Fig [1]. The age incidence was found to be between 16 years and 63 years Fig [2]. **Table 2 : Clinical Presentation of 103 cases.**

Solitary nodule	40
Diffuse	39
Multiple nodules	24
Total	103

Table 3 : The conditions which showed a predominance of Hurthle cells were classified as :-

Non - Neoplastic	
Hashimoto's	59
Nodular Colloid Goitre	10
Toxic Goitre	1
Neoplastic	
Follicular Neoplasm	13
Papillary Carcinoma	14
Hurthle cell Neoplasm	6

The cytological smears were studied on the basis of cellularity, amount of colloid, macrophages, lymphocytes, plasma cells, percentage of Hurthle cells compared with all follicular cells, percentage of single Hurthle cells ,cellular arrangement, cohesion, nuclear enlargement, nuclear pleomorphism, nucleoli and binucleation or multi nucleation.

Statistical analysis was performed with Chi-Square test. Hurthle cells in the neoplasm was compared with non neoplastic Hurthle cell lesions and statistically significant differences were noted. A P value < 0.05 was considered significant.

Of the 103 cases which showed Hurthle cells, surgery was done for 48 cases. As most of the cases were diagnosed as Hashimoto's thyroiditis and colloid goitre which did not require surgical intervention we had histopathological correlation for 48 cases. The results of which were tabulated as follows

Table 4 : Cytohistologic correlation in cases where Hurthle cells are prominent

Cytologic Diagnosis	Histologic Diagnosis	No.of Cases
Hashimoto's thyroiditis	Hashimoto's thyroiditis	6
Hashimoto's thyroiditis	Nodular colloid Goitre	2
Hashimoto's thyroiditis	Nodular colloid Goitre with thyroiditis	3
Toxic Goitre	Toxic Goitre	1
Nodular colloid Goitre	Toxic Goitre	1
Nodular colloid Goitre	Hashimoto's thyroiditis	2
Hurthle cell Neoplasm	Hurthle cell adenoma	5
Hurthle cell Neoplasm	Follicular Adenoma	1
Follicular Neoplasm	Follicular Adenoma	13
Papillary carcinoma	Papillary carcinoma	14
Total		48

For the rest of the cases, a clinical follow-up was done. Cases diagnosed as Hashimoto's thyroiditis proved to be the same by Anti body test and cases diagnosed as colloid goitre showed marked improvement with drug therapy.

The cellularity of aspirates from Hashimoto's thyroiditis varied from mild - moderate with lymphocytic infiltrate being mild - moderate. The amount of colloid was scanty in majority of the smears, with occassional smears showing moderate colloid. There was an admixture of epithelial cells, lymphocytes and plasma cells. The epithelial cells were found to be arranged in monolayered sheets and in small clusters.

In aspirates from Hashimoto's thyroiditis [Fig.3a & Fig.3b], Hurthle cells showed dark nucleus with mild - moderate nuclear pleomorphism. The nuclear chromatin pattern was bland and even. This type of atypia is called regressive atypia which is considered to be characteristic of non - neoplastic lesion.[4].Occasionally binucleated cells were seen.

Fig 3a Smears from Hashimoto"s thyroiditis showing dense sheets of lymphocytes and plasma cells(H&E) (100X)

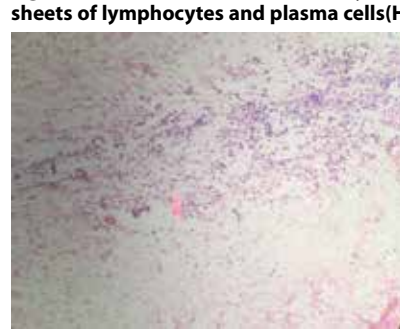
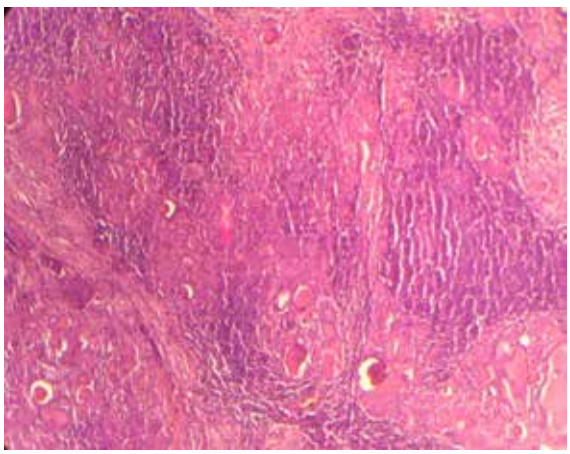
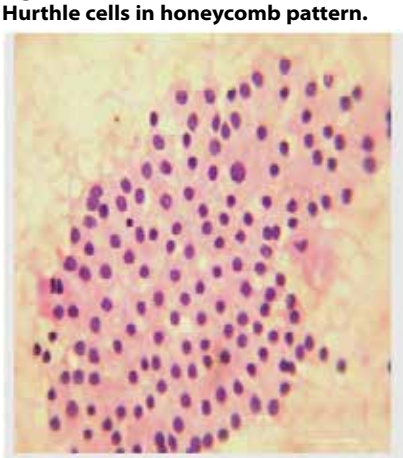


Fig 3b Sections from hashimoto's thyroiditis with lymphoid aggregates and hurthle cell metaplasia.(H&E stain) (100X)



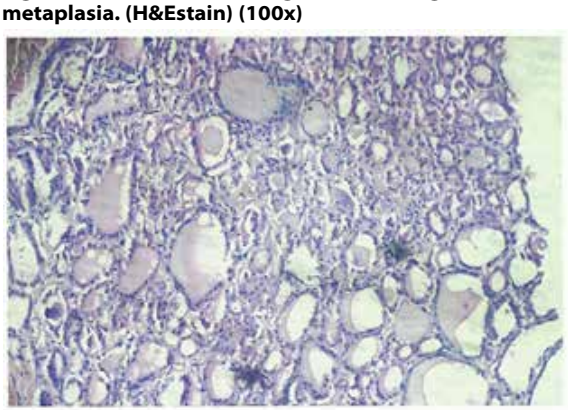
The Hurthle cell morphology in aspirates from nodular colloid goitre showed honey comb pattern of arrangement and were interspersed by regular follicular epithelial cells [Fig 4]. The differentiating feature between the Hurthle cells and regular epithelium was increase in size and the presence of abundant granular eosinophilic cytoplasm.

Fig. 4 smears from nodular colloid goiter showing Hurthle cells in honeycomb pattern.



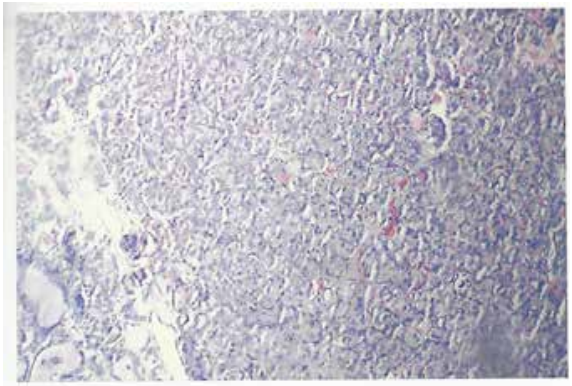
The aspirates of toxic goitre showed features of regular follicular epithelial cells arranged in flat monolayered sheets with cytoplasmic vacoulation with background showing lymphocytes and Hurthle Cells, which was proved histologically also as toxic goitre Fig [5].

Fig 5 Section from toxic goitre showing hurthle cell metaplasia. (H&Estain) (100x)



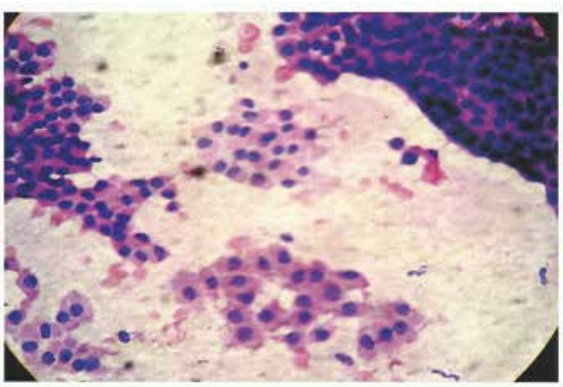
In aspirates from thyroid neoplasm the epithelial cellularity was found to be greater than that of Hashimoto's thyroiditis. Aspirates from follicular neoplasm showed micro follicular arrangement of follicular epithelial cells with a drop of colloid, in a background of Hurthle cells and lymphocytes. Histologically also the case was proved to be follicular adenoma with Hurthle cell nodule Fig [6].

Fig 6 sections showing Hurthle cell nodule from a case of follicular adenoma (H&E) (100X)



In smears from papillary carcinoma there was high cellularity with flat monolayered sheets of follicular epithelial cells which exhibited nuclear grooves and pseudo nuclear inclusions. Hurthle cells were seen in clusters Fig [7]. Three cases showed colloid and macrophages.

Fig 7 Smears from papillary carcinoma of the thyroid showing Hurthle cells.(H&Estain) (100x)



The aspirates from pure Hurthle cell lesion showed a monomorphic population of Hurthle cell arranged both in loose clusters and in singles. Nuclear enlargement and prominent nucleoli were seen in few cases. There was no colloid or lymphoplasma cytic infiltrate in the background. Such lesion proved to be well encapsulated Hurthle cell adenoma [Fig 8a & Fig 8b].

Fig. 8a smears from Hurthle cell neoplasm showing loose clusters of hurthle cells with abundant granular cytoplasm,enlarged nuclei with prominent nucleolus. (MGG stain) (400x)

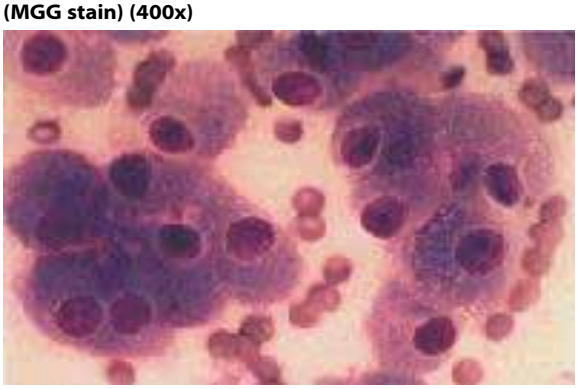
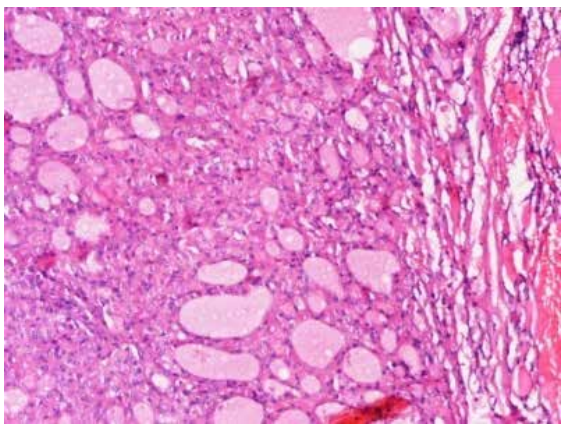


Fig. 8b Sections from Hurthle cell adenoma .(H&E stain) (100X)



There were many statistically significant cytological differences between Hurthle cell neoplasm and Non neoplastic Hurthle cell lesions.

The following features indicate Hurthle cell tumor over non- neoplastic Hurthle cell lesions. The percentage of Hurthle cell more than 90% (P value <0.05 18% neoplastic Vs 0% non neoplastic), more than 10% single Hurthle cells (18% Vs 0% respectively, P value <0.05) lymphocytes (0% Vs 90% respectively, P value <0.05) no plasma cell (0% Vs 84% respectively, P value <0.05) prominent nucleoli (9% Vs 0% respectively, P value <0.05). Nuclear enlargement (6% Vs 57% respectively, P value <0.05), Pleomorphism (12% Vs 84% respectively, P value <0.05), Cellular non cohesion (78% Vs 0% respectively, P value <0.05).

Colloid, no macrophages, cellular arrangement, binucleated and multi nucleated cells are not statistically significant parameters.

DISCUSSION

Hurthle Cells were discovered by Askanazy in 1898 in patient with Grave's disease. In 1936, Eisen studied the characteristic cytoplasmic appearance due to increased number of mitochondria in a patient with Riedel's thyroiditis

Hurthle cell nodules of the thyroid can result from non - neoplastic conditions such as Hashimoto's Thyroiditis, adenomatous Goitre and Graves disease. Conversely neoplastic nodules may be composed predominantly of Hurthle cells. They are referred to as Hurthle cell tumours and represent approximately 5% of thyroid neoplasms.

Hurthle cell neoplasms in turn can be categorized as adenomas which are usually unilateral and carcinomas which have a high incidence of bilaterality.

Kauffmann et al and Diya I. Aladeen et al[5,6] studied the significance of Hurthle cells in thyroid nodule fine needle aspiration cytology samples. They concluded that density of Hurthle cells in FNAC ranged from 20-100% the presence of more than 50% Hurthle cells in FNAC correlated with benign or malignant Hurthle cell neoplasm. Hurthle cell carcinomas displayed more than 90%. Hurthle cells in FNAC and surgery is indicated for all nodular lesions with more than 50% Hurthle cells.

Sudha R. Kini studied the difficulties in making the cytologic differentiation between surgical and non-surgical Hurthle cell lesions and had enlisted the following criteria[7].

Cytomorphology of Hurthle cell Tumours[7].

1. Monomorphic cell population.
2. Cells oval-polygonal with abundant granular cytoplasm that stains eosinophilic, cyanophilic or amphophilic.
3. Nucleus slightly eccentric, small round to oval with finely granular chromatin.
4. Prominent macro nucleolus.
5. Cells mostly in isolated or in loose groups, occasionally sheets or follicles.
6. Scanty colloid.
7. Tissue fragments with marked nuclear pleomorphism suggest malignancy. Must be differentiated from auto immune thyroiditis.
8. No inflammatory cells in the background.

Jorge L. Gonzalez et al [8] studied many statistically significant cytological differences between Hurthle cell Tumour and non-neoplastic Hurthle cell lesions, statistically significant features are

1. A high percentage of >90% Hurthle cells
2. Single Hurthle cells >10%
3. Cellular dyshesion
4. Large nucleoli
5. Significant nuclear enlargement, absence of plasma cells, macrophages and few lymphocytes.

Dr. Gita Jayaram[9] in 'Problems in the interpretation of Hurthle cell populations in Fine needle aspirates' had cases with Hurthle cell population showing features of pleomorphism in the presence of a scant number of lymphocytes. Such cases needed to be evaluated very carefully with the help of antibody tests in order to distinguish Hurthle cell lesions requiring surgical intervention from those that do not.

Sudha R. Kini et al [7] has pointed out that 'Horn in 1951 stated that the papillary or follicular cancers composed of Hurthle cells do not behave differently from the usual follicular or papillary carcinomas. He felt that the architectural pattern rather than the cell type predicted the behaviour of the tumour.

Stefan E. Pambucian et al[10] studied that nucleolar features such as size, variation in size and roundness may be more effective than cellular or nuclear features in differentiating Hurthle cell adenomas and Hurthle cell carcinomas in Fine needle aspiration cytology smears.

The diagnosis of Hashimoto's thyroiditis on fine needle aspiration cytology samples is made when lymphoid and Hurthle cell components are present in varying proportions. Problems may arise when the proportion of these two cell components are markedly deviated.

Fine needle aspiration was successful in detecting Hashimoto's thyroiditis in six cases. In three cases Hashimoto's thyroiditis was diagnosed but did not sample the associated lesion. These three cases presented as multi nodular goitre. Sampling error in these cases stresses the importance of adequate sampling from several areas of thyroid lesions especially when there is an associated nodule [11].

In the remaining two cases of Hashimoto's thyroiditis, histologically nodular colloid goitre was reported. A small population of lymphoid cells from peripheral blood was considered as the source of these cells causing misinterpretation. According to Laurie MacDonald [11], A diagnosis of lymphocytic thyroiditis should not be made when only a few lymphocytes are present.

Dr.Gita Jayaram[9] in "Problems in the interpretation of Hurthle cell populations in fine needle aspirates" have also encountered these Hurthle cells showing features of pleomorphism in the presence of scant number of lymphocytes. Such cases needs to be evaluated very carefully with the help of antibody tests.

The aspirates from non - neoplastic Hurthle cell nodules of Nodular goitre tend to exhibit tissue fragments of Hurthle cells that display a 'Honey comb' pattern. This is in contrast to Hurthle cell neoplasms in which a dissociated pattern are seen. Also in non - neoplastic lesions, the Hurthle cells less commonly display the characteristic nuclear morphology. Macronucleolus is infrequently seen. Other features that may help in differentiation are the admixture of regular follicular epithelium and the frequent occurence of pyknotic nuclei in Hurthle cells.

In two cases of nodular goitre Hurthle cells are associated with ordinary follicular cells arranged in large sheets, macrofollicles and abundant colloid. The amount of colloid is not a statistically significant parameter [8].

Hashimoto's thyroiditis typically have a scant colloid. But one case

which had abundant colloid was histologically proved as Hashimoto's thyroiditis. Nodular goitre may also have scant colloid with Hurthle cell. This explains that colloid is not a significant parameter in differentiating Hurthle cell lesion from non - neoplastic Hurthle cell lesion.

According to Gita Jayaram[9] in "Problems in the interpretation of Hurthle cell populations in fine needle aspirates" have encountered the hurthle cells in toxic Goitre, Follicular neoplasms and papillary carcinoma. In these conditions the problem is alleviated by the presence of features specific to the predominant lesion.

In the case of follicular neoplasm, the thyroid follicular epithelial cells are seen in clusters and in micro acinar groupings with colloid. Hurthle cells are seen in small groups. Histologically well encapsulated follicular adenoma with Hurthle cell component are seen.

The presence of Hurthle cells in papillary carcinoma does not change the usual behaviour of papillary carcinoma. The architectural pattern rather the cell type predicted the behaviour of the tumour[7]

The accurate diagnosis of Hurthle cell tumour by fine needle aspirate is very important. The aspirates from Hurthle cell lesion show monomorphic cells with loosely cohesive tissue fragments as well as in singles. The nuclear chromatin is finely granular with prominent nucleoli. There were no inflammatory cells in the background. 5 cases of Hurthle cell tumour were diagnosed Histologically as well encapsulated Hurthle cell adenoma. There was no evidence of invasion. One case turned out to be follicular adenoma with Hurthle cell component.

The results of our study were statically compared with the study of "Fine Nedle Aspiration of Hurthle cell lesions" by Gonzalez [8].

Table 5 :Statistically Significant Cytologic Features Favoring Hurthle Cell Tumour in our study

Cytologic Feature	P Value	% of cases of HCT	% of Cases of NNHCL
Single Hurthle cells (>10%)	<0.05	18%	0%
Hurthle Cells of total follicular cells (>90%)	<0.05	18%	0%
Large nucleoli	<0.05	9%	0%
Nuclear enlargement	<0.05	6%	57%
Nuclear pleomorphism	<0.05	12%	85%
No plasma cells	<0.05	100%	15%
Lymphocytes	<0.05	0%	90%
Cellular non cohesion	<0.05	78%	0%

Table 6: Statistically Significant Cytologic Features Favoring Hurthle Cell Tumour in Gonzalez, Series

Cytologic Feature	P Value	% of cases of HCT	% of Cases of NNHCL
Single Hurthle cells (>10%)	<0.001	84%	21%
Hurthle Cells of total follicular cells (>90%)	<0.001	100%	21%
Large nucleoli	<0.001	79%	0%
Nuclear enlargement	<0.001	47%	0%
Nuclear pleomorphism	<0.001	47%	0%
No macrophages	<0.04	68%	53%
No plasma cells	<0.01	58%	11%
Lymphocytes	<0.001	89%	37%
Cellular non cohesion	<0.001	95%	16%

Nuclear enlargement and pleomorphism may be a common feature in non neoplastic thyroid aspirates [12]. This might be the reason for the increased percentage of nuclear atypia seen in non neoplastic lesion in our series, also the distribution of cases studied by us were more of non - neoplastic than neoplastic. The architecture of Hurthle cell groups, cellularity, amount of colliod, presence of multinucleated Hurthle cells and no macrophages appeared to be of no value.

CONCLUSION

From our study it was observed that the cytological features of Hurthle cells varied in different lesions of the thyroid, thus enabling us to differentiate between non-neoplastic and neoplastic lesions by way of which we could guide the clinicians regarding further therapeutic management. The following characteristics are statistically predictive of Hurthle cell tumour over non neoplastic Hurthle cell lesions. A high percentage of (> 90%) Hurthle cells, more than 10% Hurthle cells being single, cellular non - cohesion, prominent nucleoli, nuclear enlargement and nuclear pleomorphism, absence of plasma cells and lymphocytes.

These features help in identification of Hurthle cell nodules that are likely to be neoplastic and require surgical excision and careful histologic evaluation.

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