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Original Research Article

RECLASSIFICATION OF THYROID LESIONS BASED ON THE BETHESDA SYSTEM BY FINE NEEDLE ASPIRATION CYTOLOGY: A 2 YEAR STUDY FROM A TERTIARY CARE CENTRE IN NORTH-EAST INDIA

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Abstract

Background: Thyroid gland is affected by a vast array of disorders like developmental, inflammatory, hyperplastic and neoplastic disorders. Both non-neoplastic and neoplastic diseases affect it and led to diffuse or nodular enlargement. FNAC is widely considered as the diagnostic technique of choice in the assessment of thyroid lesions. In the Bethesda system for reporting thyroid cytopathology (TBSRTC), the six diagnostic categories have been designated one to six roman numbers. A thyroid FNA specimen is considered to be satisfactory for evaluation (and benign), at least 6 groups of benign follicular cells are required, and each group composed of at least 10 cells.

Methods: A two year retrospective cross sectional study was conducted. Patients attending cytology out-patient department, were the study population. Consent was obtained from all the patients before the start of the procedure. Twenty ml syringe with 24 gauge needle fitted in Cameco handle was used for aspiration. Prepared smears were stained with Giemsa stain. Any cystic fluid thus withdrawn from the swelling was centrifuged and the deposit was studied microscopically after spreading.

Results: A total of 539 thyroid swelling were aspirated during the study period. Of 539 cases 88% of cases were reported in females and 12% of cases were reported in males. Ninety percentage of cases were reported under benign category. Twenty five(4.6%) cases were reported as malignant during the study period, out of which 23(4.2%) cases were reported as papillary carcinoma. Papillary carcinoma constitutes the most common malignant lesion reported during the study period.

Conclusion: The Bethesda system provides a standardized nomenclature for thyroid cytopathology reporting with improved interobserver reproducibility. Facilitates better understanding between cytopathologist and clinicians for uniform and proper management.

Key words: Thyroid, Fine needle aspiration cytology (FNAC), The Bethesda system.

Introduction:

The thyroid gland is a vital butterfly shaped endocrine gland situated in the lower part of the neck. It is present in front and sides of the trachea, inferior to the larynx. It is a gland consisting of two lobes, the right and the left lobes joined together by an intermediate structure, the isthmus. Sometimes a third lobe called the pyramidal lobe projects from the isthmus. The thyroid gland is divided into lobules, each lobules consist of a large number of typical units called thyroid follicles. The thyroid follicles are the structural and functional units of a thyroid gland. These are spherical, and the wall is made up of a large number of cuboidal cells, the follicular cells. These follicular cells are the derivates of the endoderm and secrete thyroid hormone. In between these thyroid follicles or within the wall of the thyroid follicles, we find the small C cells, also known as parafollicular cells. These are derived from neural crest cells and secrete polypeptide hormone known as calcitonin.[1]

Thyroid gland is affected by a vast array of disorders like developmental, inflammatory, hyperplastic and neoplastic disorders. The incidence of palpable thyroid swelling is 4-7%. A thyroid enlargement whether diffuse or in the form of a nodule has to be investigated to rule out neoplasm. Only about 20% of patients undergoing thyroid surgery for suspicious of carcinoma actually show the histology of malignancy.[2] The term “thyroid nodule” refers to a distinct lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma. They are more common among women. In India the prevalence of a palpable thyroid nodule in the community is about 12.2%, according to a recent study. However, thyroid cancer is quite rare, and the incidence is

8.7 per 100000 people per year, though this seems to be increasing over the years.[3]

Both non-neoplastic and neoplastic diseases affect it and led to diffuse or nodular enlargement. Non-neoplastic lesions are more common n thyroid like goitre, thyroiditis and Grave's disease. Neoplastic lesions like follicular neoplasms, papillary carcinoma, and medullary carcinoma though less common may show overlapping clinical features with non-neoplastic lesions. There are various diagnostic modalities to work up thyroid diseases which include thyroid function tests, radioisotope scan, ultrasonogram (USG) and fine needle aspiration cytology (FNAC).[4]

FNAC is widely considered as the diagnostic technique of choice in the assessment of thyroid lesions. It is simple, minimally invasive and an ideal fine line diagnostic test. The thyroid FNAC greatly helps in the evaluation of inflammatory, infectious and neoplastic conditions. It helps especially to distinguish non neoplastic from neoplastic swellings.[5] FNAC has an essential role in the evaluation of euthyroid patients with a thyroid nodule as it reduces the rate of unnecessary thyroid surgery for patients with benign nodules and appropriately triages patients with thyroid cancer to appropriate surgery. Given the high prevalence of nodules combined with the impracticality of surgically excising all nodules, FNA plays a vital role as a screening test. Every patient with a palpable or incidental thyroid nodule is a candidate for FNA. A nodule that appears either iso- or hypo- functioning on radionuclide scan should be considered for FNA based on ultrasound findings. However despite its widespread use, thyroid FNA currently suffers from a reporting confusion: multiplicity of category names, descriptive reports without categories and variable surgical pathology terminology.[6] A substantial number of thyroid nodules (20%-25%) are classified in the so called intermediate category (atypia of undetermined significance/ follicular lesion of undetermined significance [AUS/FLUS], follicular neoplasm/ suspicious for follicular neoplasm [FN/SFN] or suspicious for malignancy [SM]) on preoperative FNA, which poses difficulties for management. The American national institutes of health system for reporting thyroid FNAC (Bethesda system) aimed to improve diagnosis of indeterminate thyroid nodules. Its strategies include: 1. More precise and defined standardised nomenclature and morphological criteria; 2. The indeterminate category was divided into lower-risk (AUS/FLUS); intermediate risk (FN/SFN) and higher risk (SM); 3. Risk of malignancy (ROMs) were estimated in each cytological category to serve as a quality control guide; 4. The target number of AUS/FLUS was set at less than 7% to minimise its over use; and 5. Clinical management of cytological categories were defined for improved communication among patients, cytopathologists and clinical doctors. [7]

In the Bethesda system for reporting thyroid cytopathology (TBSRTC), the six diagnostic categories have been designated one to six roman numbers. The categories are as follows: i. Nondiagnostic, ii. Benign, iii. Atypia/follicular lesion of undetermined significance, iv. Follicular neoplasm/suspicious for a follicular neoplasm, v. Suspicious for malignancy, vi. Malignant. A criteria for adequacy of a cytological preparation has been defined in Bethesda as : 'A thyroid FNA specimen is considered to be satisfactory for evaluation (and benign), at least 6 groups of benign follicular cells are required, and each group composed of at least 10 cells.'[8]

After the implementation of TBSRTC, various authors have described their experience with Bethesda. Most of these studies have been from the western countries where epidemiology and demography of thyroid lesions is usually different.[9] Since there have not been many studies from North-East India, this study was undertaken to compare our in-house classification with TBSRTC and access the feasibility of using Bethesda in our clinical setting.

Aims and Object:

To reclassify various cytomorphological lesions of the thyroid according to the Bethesda system for reporting of thyroid cytopathology (TBSRTC).

Methods:

A two year retrospective cross sectional study was conducted from January 2016 to December 2017 in the Department of Pathology, Regional Institute of Medical Sciences, Imphal, Manipur. Patients attending cytology out-patient department, were the study population. Consent was obtained from all the patients before the start of the procedure. All relevant clinical details were noted. No anaesthetic drug was used as it was a minimally painful procedure. In the supine position with the neck moderately extended, the swelling was fixed. Twenty ml syringe with 24 gauge needle fitted in Cameco handle was used for aspiration. The needle was inserted in a near vertical direction with the plunger of the syringe in resting position. After checking the position of the needle in the predetermined site the plunger was retracted for exerting negative pressure. To obtain the greatest possible yield, the needle was moved back and forth within the lesion in different directions with the negative pressure maintained in different directions. When the aspiration was complete the plunger was released to eliminate negative pressure before the needle was withdrawn. Detaching the needle from the syringe, the plunger was withdrawn to allow 2-3 ml of air in the syringe and the needle was reattached and then the material was blown out onto a clean dry slide by pushing the plunger. With the help of another slide the material was spread and air dried. Prepared smears were stained with Giemsa stain. Any cystic fluid thus withdrawn from the swelling was centrifuged and the deposit was studied microscopically after spreading.[10]

Statistical Analysis:

In the present study, data has been entered and analysed using IBM SPSS statistic 24. Here we have studied the age range and the frequency distribution of the cases in percentage according to the Bethesda system.

Results:

A total of 539 thyroid swelling were aspirated during the study period. All the cases were reclassified according the Bethesda system for reporting thyroid cytopathology.

Table 1: Sex wise distribution of cases (N=539)

Sex	No. of cases	Percentage (%)
Male	67	12
Female	472	88
Total	539	100

As shown in table 1, of 539 cases 88% of cases were reported in females and 12% of cases were reported in males, with a male: female ration of 1:7.

Table 2: Age wise distribution of cases (N=539)

Age group	No. of cases	Percentage (%)
<10	11	2
11-20	52	9.6
21-30	93	17.2
31-40	112	20.7
41-50	122	22.6
51-60	84	15.5
61-70	46	8.5
71-80	12	2.2
81-90	07	1.2
Total	539	100

As shown in table 2, the maximum number of cases were reported in 41-50 yrs. age group around 22.6% followed by 31-40 yrs. age group around 20.7%.

Table 3: Reclassification of Pre-Bethesda diagnosis into the Bethesda diagnosis (N=539)

Bethesda diagnosis							
		I US/ND	II Benign	III AUS/FLUS	IV FN/SFN	V SFM	VI Malignant
Pre-Bethesda diagnosis	Total						
Colloid goitre	264	00	264	00	00	00	00
Lymphocytic thyroiditis	159	00	159	00	00	00	00
Hashimoto's thyroiditis	24	00	24	00	00	00	00
Subacute thyroiditis	11	00	11	00	00	00	00
Adenomatoid/hyperplastic nodule	12	00	12	00	00	00	00
Thyroglossal cyst	13	00	13	00	00	00	00
FLUS	01	00	00	01	00	00	00
Follicular neoplasm	08	00	00	00	08	00	00
Follicular neoplasm (Hurtle cell type)	01	00	00	00	01	00	00
Suspicious of malignancy papillary	03	00	00	00	00	03	00
Suspicious of malignancy anaplastic	03	00	00	00	00	03	00
Papillary thyroid carcinoma	23	00	00	00	00	00	23
Medullary thyroid carcinoma	01	00	00	00	00	00	01
Undifferentiated/Anaplastic thyroid carcinoma	01	00	00	00	00	00	01
Unsatisfactory	15	15	00	00	00	00	00
Total	539	15	483	01	09	06	25

US/ND→ unsatisfactory/non-diagnostic
AUS/FLUS→Atypical of undetermined significance or follicular lesion of undetermined significance
FN/SFN→ Follicular neoplasm or suspicious of follicular neoplasm
SFM→ suspicious of malignancy
As shown in table 3, all the 539 cases were reviewed and pre-Bethesda diagnosis was reclassified into Bethesda diagnosis. Of 264 cases of colloid goitre, 159 cases of lymphocytic thyroiditis, 24 cases of hashimoto's thyroiditis, 11 cases of sub-acute thyroiditis, 12 cases of adenomatoid/hyperplastic nodule and 13 cases of thyroglossal cyst of pre-Bethesda diagnosis were clubbed together into the Bethesda category II (Benign).

Table 4: Distribution of cases according to the Bethesda system 0(N=539)

Bethesda category	No of cases	Percentage (%)
I	15	2.8
II	483	89.6
III	1	0.2
IV	9	1.7
V	6	1.1
VI	25	4.6
Total	539	100

As shown in table 4, of 539 cases 483(89.6%) cases were reported as benign which constitutes the most common category reported during the study period. Nine(1.7%) cases were reported as follicular neoplasm or suspicious of follicular neoplasm and out of 9(1.7%) cases 1(0.2%) case was reported as follicular neoplasm or suspicious of follicular neoplasm Hurtle cell type. Twenty five(4.6%) cases were reported as malignant during the study period, out of which 23(4.2%) cases were reported as papillary carcinoma. Papillary carcinoma constitutes the most common malignant lesion reported during the study period.

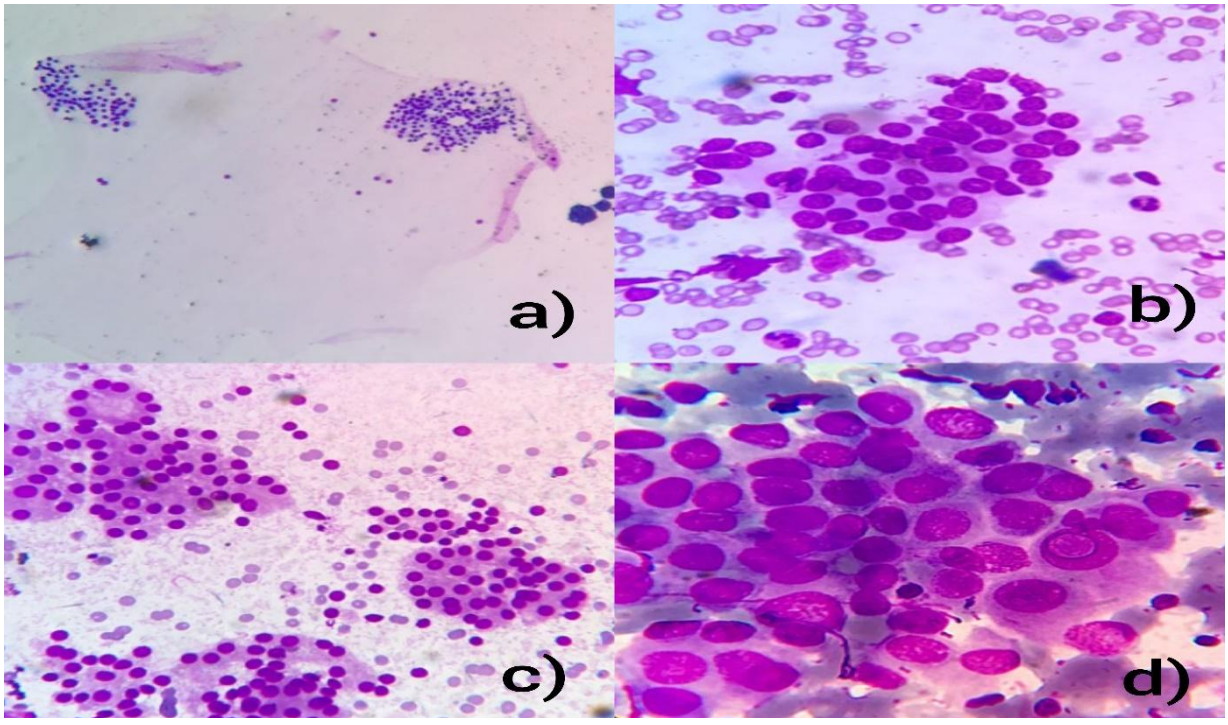

Fig 5: Photomicrographs of cytology of a) colloid goitre showing benign thyroid follicular cells in sheet in the background of thin and thick colloid [Giemsa, 100X], b) Lymphocytic thyroiditis showing impingement of thyroid follicular cells by lymphocytes [Giemsa, 400X], c) Follicular neoplasm/Suspicious of follicular neoplasm showing thyroid follicular cells in repetitive microfollicular pattern [Giemsa, 400X], d) papillary thyroid carcinoma showing nuclear membrane irregularity and nuclear cytoplasmic pseudo-inclusion [Giemsa, 1000X].

Discussion:

Interpretation of thyroid FNA is challenging because there is comparatively little difference in the morphologic features of the many non-neoplastic and neoplastic conditions of the thyroid, and there is variability in FNA specimen preparation and interpretation. Thyroid FNA has traditionally been performed by various aspirators: Endocrinologists, surgeons, radiologists, and cytopathologists, resulting in various specimen quality. Before TBSRTC was introduced, reports were largely descriptive, with a multiplicity of category names, descriptive reports (no categories), or the use of surgical pathology terminology.[11]

The advantage of TBSRTC is that it is systematic, and has achieved the goal of standardization and improving thyroid cytopathology reporting. However, the category of AUS/FLUS is the most controversial, due to its heterogeneity, leading to confusion among clinicians regarding management.[9] Predicts the prognosis by estimating the malignant potential of the individual category. To follow standard management protocol.

Non diagnostic/ unsatisfactory category have a risk of malignancy around 5-10% and the usual management protocol is repeat FNA with ultrasound guidance.[12] FNA of thyroid is considered to be nondiagnostic or unsatisfactory, when the aspirate contains cyst fluid only, virtually acellular specimen, and specimen obscured by blood, clotting artefacts, etc.[8] In the current study around 3% of cases were reported under this category which is similar to the study conducted by Puri R et al[5].

Risk of malignancy of benign category constitutes around 0-3% and the usual management protocol involves clinical and sonographic follow-up.[12] Benign category constitutes the most common lesion encountered in the current study constituting around 89.6%, which is in concordance to the study conducted by Puri R et al[5] in whose study the percentage of benign category constituting around 92%.

Benign results are further subclassified as benign follicular nodules, thyroiditis, or other less common entities. The benign follicular nodules (BFN) encompasses a group of benign lesions with similar cytologic features that are classified histologically as nodules in nodular goitre (NG), hyperplastic (adenomatoid) nodules, colloid nodules, nodules in Grave's disease, and a subset of follicular adenomas (those of macrofollicular type). The distinction among these histologic entities may not possible on cytology. However, it is less significant inn practice as these lesions are all benign. The designation 'benign follicular nodule' applies to a cytologic sample that is adequate for evaluation and consists predominantly of colloid and benign appearing follicular cells in varying proportions, Hurtle cells and macrophages. Depending on clinical presentation, a more specific term like colloid nodule, nodular goitre, hyperplastic or adenomatous nodule and Grave's disease may be used.[8]

The most common lesion encountered under the benign category in the current study is colloid goitre constituting around 49.2%, which is similar to the study conducted by Laishram R et al[13] and Sekhar A et al[14].

AUS/FLUS constituting around 0.1% in the current study, no cases under category III was detected in the study conducted by Puri R et al[5]. Khadatkar As et al[4] reported around 3% of cases under category III in there study. The risk of malignancy of category III constitutes around 10-30% and the usual management protocol involves repeat FNA, molecular testing, or lobectomy.[12] This category is reserved for specimens that contain cells with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm, suspicious for malignancy or malignant. There is a prominent population of micro follicles which fall short for the diagnosis of 'Follicular neoplasm/suspicious for follicular neoplasm'. There is a predominance of Hurtle cells in a sparsely cellular aspirate with scant colloid.[8]

FN/SFN constitutes around 1.6% in the current study, which is similar to the study conducted by Puri R et al[5] and Khadatkar AS et al[4]. Risk of malignancy of category IV constitutes around 25-40% and the usual management protocol involves molecular testing and lobetomy.[12] The specimens are cellular with scant or without colloid. The follicular cells are arranged as micro follicles; designation must be limited to crowded, flat groups of less than 15 follicular cells arranged in a circle that is at least two thirds complete. Nuclei are usually round and mildly hyperchromatic and nucleoli are occasionally seen. Cases with features of papillary thyroid carcinoma are excluded from this category. FN/SFN Hurtle cell type is used for the specimens containing almost exclusively Hurtle cells with architectural alteration manifested by syncytial fragments, loose clusters or single cells.[8,15]

In the current study around 1.1% of cases were reported under category V. Risk of malignancy of this category is around 50-75% and the usual management protocol involves near total thyroidectomy or lobectomy.[12] This category is used when specimens show some features that are strongly suspicious, but not definitive for malignancy. Sub-classifications include 1) suspicious for papillary carcinoma, 2) suspicious for medullary carcinoma, 3) suspicious for lymphoma, and 4) suspicious for malignancy, not otherwise specified.

Category VI constitutes around 4.6% in the current study which is similar to the study conducted by Puri R et al[5] and Khadatkar AS et al[4]. Risk of malignancy is around 97-99% and the usual management protocol involved near total thyroidectomy or lobectomy.[12] Papillary carcinoma is the most common lesion reported under category VI in the present study constituting around 4.2% which is similar to the study conducted by Sekhar A et al[14]. For conventional and variants of papillary carcinoma, TBSRTC illustrates the following cytomorphological features: hypercellularity, papillae and/or syncytial tissue fragments, follicular cells

with characteristic nuclear features including nuclear enlargement, oval or irregular shaped nuclei with crowding/overlapping/moulding, intranuclear longitudinal grooves and cytoplasmic pseudo-inclusions, powdery chromatin, marginally located micro-nucleoli, Psammoma bodies, and multinucleated giant cells.[15]

The Bethesda thyroid conference has explored the potential of ancillary tests, immunomarkers and molecular tools applied on FNA samples to identify thyroid cancers. Molecular testing using markers such as BRAF, Ret/PTC, RAS and paired box gene (PAX) peroxisome proliferator activated receptor-c (PPAR-c) shows more promise for wider applicability in thyroid cytodiagnosis.[8]

Conclusion:

The Bethesda system provides a standardized nomenclature for thyroid cytopathology reporting with improved interobserver reproducibility. Facilitates better understanding between cytopathologist and clinicians for uniform and proper management. Allows easy and reliable sharing of data from different laboratories. Therefore, we recommend routine use of TBSRTC for reporting thyroid cytopathology for initial workup of patients with thyroid nodule.

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