European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 06, 2022

Original Research Article

Cytological evaluation of thyroid lesions and its correlation with thyroid function tests-in the era of the Bethesda system for reporting thyroid cytology

[1]Dr. Chandni Bhailal Patel, [2]Dr. Mitsu Vaishnav, [3]Dr. Sameep Garg

[1,2,3] Department of Pathology, NAMO Medical Education & Research Centre, Silvassa, Dadra & Nagar Haveli, India

Corresponding Author:
Dr. Sameep Garg

Abstract

Background: Thyroid dysfunction is very common, especially in females. Fine needle aspiration cytology (FNAC) is considered gold standard for evaluating thyroid nodules. The study was done with an aim to correlate cytological and hormonal level findings in thyroid lesions and also to categorize lesions using the Bethesda system for reporting thyroid cytology (TBSRTC).
Materials and Methods: This was an observational, retrospective study which included the data of two years from a tertiary care hospital in Silvassa. Data of all the patients referred for FNAC from ENT/Surgery outpatient department for thyroid lesions were included in the study. The data from their Thyroid function tests (TFT) measuring the levels of triiodothyronine, thyroxine and thyroid stimulating hormone was also collected. The FNAC results were classified based on the TBSRTC guidelines. The data was reported using descriptive statistics.
Results: A total of 186 cases irrespective of gender and age were included in the study for evaluation. The mean age of the patients was 40.8 ± 4.62 years.
The male: female ratio was 1:4.8 showing female preponderance. The most common thyroid lesions were benign category with 163 cases. 2 cases were malignant, both being papillary carcinoma. Out of total 163 benign thyroid lesions, 121 cases were consistent with benign follicular nodule, 39 cases with lymphocytic thyroiditis and 3cases with Granulomatous thyroiditis. Among the 121 cases of benign follicular nodule, TFT results of 71 were available, out of which, 48 were euthyroid, 12 were hyperthyroid and 11 were hypothyroid. Most of the patients of lymphocytic thyroiditis had abnormal TFT.
Conclusion: Hormonal status alone does not help in screening of thyroid lesion. Cytology is the gold standard for diagnosing thyroid lesion and reporting them using TBSRTC is quick and efficient.

Keywords: Fine needle aspiration cytology, thyroid nodule, thyroid function tests

Introduction

Thyroid is a butterfly-shaped endocrine gland located in the neck. Thyroid secretes two hormones: Triiodothyronine (T3) and Thyroxine (T4). These hormones are necessary for normal survival and functioning of cells of the body. The thyroid is an important gland

ISSN 2515-8260 Volume 09, Issue 06, 2022

involved in the metabolism, growth, development, and maintenance of the internal environment. Thyroid dysfunction is very commonly encountered in clinical practice. Thyroid disorders are one of the most common endocrine disorders worldwide, especially in females. Thyroid function tests (TFT) which evaluates the levels of T3, T4 and thyroid stimulating hormone (TSH) are considered the gold standard for the diagnosis of thyroid dysfunction. TSH is considered the most important indicator for the evaluation of thyroid function [1].

Thyroid nodules are common and affect up to 7% population of the United States [2]. Great majority of these nodules are benign. Thyroid nodules could lead to either hyperthyroidism or hypothyroidism. Fine needle aspiration (FNA) is considered an essential tool in providing a rational approach to the clinical management of thyroid nodules. The result of FNA can determine whether a thyroid nodule should be followed clinically or undergo surgical excision [2]. Simplicity, diagnostic accuracy and cost effectiveness have given FNA the status of the first line diagnostic test in the preoperative evaluation of thyroid lesions [3].

The terminology used for reporting thyroid cytology has varied markedly. These creates confusion amongst clinicians to interpret cytology report and consequently clinical management is hampered. To address these issues, National Cancer Institute (NCI) of US organized a conference at Bethesda Maryland in the year 2007 [4]. This led to the development of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). This system uses 6 categories which the cyto-pathologist can use to communicate thyroid FNA interpretations to the referring physician. These terms are universal, succinct, unambiguous, and helpful clinically [5]. Thus, this study was done with an aim to correlate the cytological findings with the hormonal levels on TFT in patients with thyroid nodules. Also, percentage of different thyroid lesions based on Bethesda system of reporting thyroid cytopathology will be evaluated.

Materials and Methods

This was an observational, retrospective study conducted by cytology section of Department of Pathology at NAMO Medical Education and research Institute, Dadra and Nagar Haveli, Silvassa. The data was collected for a period of two years from January 2020 to December 2021. The study was commenced after obtaining permission from the institutional ethics committee.

Study procedure

The study included data from all patients of both genders and all ages presenting with diffuse or nodular thyroid swelling. Demographic and clinical details of the patients were recorded on a pre-approved, pre-validated data sheet. Data of thyroid function tests, i.e. the levels ofT3, T4 and TSH hormones was recorded. In all the patients, FNA using a 22 or 23-gauge needle was done following standard procedure under aseptic precautions. Smears were made from the aspirates and were immediately fixed with methanol and stained with H&E and PAP stains. Smears were evaluated by pathologist and categorized according to The Bethesda system of reporting thyroid cytopathology (TBSRTC). The Thyroid Function Test (TFT) profile (T3, T4, TSH) was performed using Siemen's Advia centaur CP Chemiluminescence immunometric assay method. The reference range for T3 (triiodothyronine) -0.6-1.81 ng/ml, Free T3 (triiodothyronine) -2.18-3.98pg/ml;T4 (Thyroxine)-4.5-12.6 µg/dl, Free T4 (Thyroxine)-0.76-1.46ng/dl; TSH- 0.55 - 4.78 µIU/ml [6].

ISSN 2515-8260 Volume 09, Issue 06, 2022

Data analysis

The data was collected and evaluated using Microsoft Excel 2016. Descriptive statistics such as mean, standard deviation and percentage was used to report the results.

Results

A total of 186 patients with thyroid lesions irrespective of their age and sex, were referred for FNAC from ENT/Surgery OPD or admitted to the ward during the two year study period. The mean age of the patients was 40.8 ± 4.62 years. Gender distribution of thyroid lesions showed female preponderance, with 154 females and 32 males and had a male: female ratio of 1:4.8.
The distribution of 186 cases of thyroid FNAC according to TBSRTC guidelines is shown in Table 1. The most common thyroid lesions were benign in 163(87.6%) patients. Out of 186, 2(1.1%) cases were of malignant category which was papillary carcinoma of thyroid. When only cyst fluid was aspirated without cellularity or colloid and smears with blood only, the cases were categorized in Category I. Out of total163 benign thyroid lesions, 121(65.1%) cases were consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule), 39(20.9%) cases were consistent with lymphocytic (Hashimoto) thyroiditis and 3(1.6%) cases of granulomatous (subacute) thyroiditis.
Thyroid hormonal profile was available for 118 out of 186 cases. More than half pf the patients (59.3%, n = 70) were euthyroid; 27 (22.9%) were hypothyroid and 21 patients (17.8%) were hyperthyroid.
Among the patients with benign follicular nodule, majority were euthyroid (48/71), (12/71) were of hyperthyroidism and (11/71) show hypothyroidism. In category II, among the patients with lymphocytic thyroiditis, most of the patients had abnormal thyroid function test i.e., either hypothyroidism (14/29) or hyperthyroidism (5/29) and few were euthyroid (10/29). Subacute thyroiditis both cases had hyperthyroidism on TFT (2/2).
In contrast, from category III to VI majority cases were euthyroid. Only 2 cases had hypothyroidism on TFT. None of the malignant cases presented with hyperthyroidism. Table 2 shows TFT results distributed along with TBSRTC guidelines.

Discussion

Thyroid swelling is a very common endocrine disorder, especially in females worldwide. Due to easy availability of newer investigations, it has become possible to diagnose these swelling early. Thyroid enlargement, whether diffuse or nodular, leads to a battery of investigations, mainly to rule out the possibility of a neoplasm or thyroiditis. FNAC is the first line of investigation and other investigations like ultra-sonography (USG), TFT, thyroid scan and antibody levels are done subsequently for appropriate management [7].
According to the guidelines of American Thyroid Association, serum estimation of TSH should be part of initial assessment of thyroid swellings. Additional evaluation is required when overt or subclinical hyperthyroidism is present. A higher serum TSH level, is usually associated with increased risk of malignancy in a thyroid nodule, as well as more advanced stage thyroid cancer [8].
The mean age in the present study was 40.8 years, which correlates well with the studies conducted by Thakor T *et al.* [9], Jain V *et al.* [10]and Das MK *et al.* [11] where the mean age at presentation was 39.6 years, 41.3 years and 40.4 years respectively. The male: female ratio in the present study was 1:4.8, which correlates well with the studies conducted by Thakor T *et al.* [9] and Jain V *et al.* [10] which reported a male: female ratio of 1:5.3 and 1:6.2, respectively.
Table 3 shows the distribution of cases according TBSRTC categories obtained in present study as compared to previously published studies. It was seen that the distribution of cases as

ISSN 2515-8260 Volume 09, Issue 06, 2022

per the six-tier Bethesda system in our study differed from that mentioned in Table 3 studies [3, 5, 9, 10, 12] with the percentage of cases in the benign category being higher and that in the non-diagnostic and Atypia or Follicular Lesion of Undetermined Significance categories being lower. The reason for the number of cases in the benign category being higher can be attributed to the fact that, our institute patients come directly without referral. So, a large population, representative of the general population, is encountered in our institute. Therefore, it is reflected proportionately in our study. A second reason could be at our institute, procedure of FNAC is easily accessible to the economically backward areas of the society for whom the test is performed at very minimal cost.

Most common thyroid lesions of Bethesda category II in our study were benign follicular nodule and majority were euthyroid (67%) which is similar to findings stated by Jain V *et al*. (88.1%) [10].

On hormonal assay, majority (48.3%, n = 14) of patients of lymphocytic thyroiditis in present study showed hypothyroidism, suggesting an advanced stage of the disease at the time of diagnosis and represented destructive phase of the disease. There were 5 cases of hyperthyroidism (17.2%) in the study indicating Hashitoxicosis which is a transient hyperthyroid phase. It is due to acute aggravation of thyroid autoimmunity induced destruction of thyroid follicles. Further, 10 cases were euthyroid (34.5%) with normal T3 and T4 levels indicating disease in phase of evolution. These findings were correlated with many studies [13, 14, 15, 16].

Subclinical hypothyroidism is the state where T3 and T4 are normal with TSH being above the defined upper limit of the reference range. It represents an early phase of hormonal imbalance. In this study, 24.1% (7/29) of the cases presented with subclinical hypothyroidism, similar to a study of Megalamane S. *et al*. (21.4%) [13] However, Gupta C *et al*. [14] found 11 cases (14.10%) in their subjects, which is lower compared with our study. The lower rates again could be attributed to assessment of the patients in different stages of thyroiditis.

The incidence of malignancy in Hashimoto's thyroiditis (HT) is documented to vary from 0.4% to 28% [17, 18]. The most commonly encountered neoplasms in association with HT are papillary thyroid carcinoma (PTC) and primary thyroid lymphoma [17]. Similar observations were made in our study. We came across only one case of HT with PTC-micro-carcinoma in our study. We missed definitive diagnosis because it was only 0.4 cm focus on histopathology and on radiology diagnosis of diffuse thyroid disease was given so aspiration from neoplastic focus was not possible. Another case of benign thyroid nodule, was finally diagnosed on histopathology as a follicular adenoma because cellularity and other features of follicular neoplasms are not fulfilled on cytology.

The presence of chronic inflammation in HT may act as an initiating factor for carcinogenesis could be a potential explanation for the association of HT with malignancy. Another hypothesis is elevated levels of TSH found in hypothyroid patients with HT may stimulate follicular epithelial proliferation, thereby promoting the development of papillary carcinoma [19]. In our study 2 out of 5 cases show elevated TSH level which is correlated with the study by Jain V *et al*. [10] which reported higher TSH level in 9 out of 12 cases.

There is an overlap of clinical, radiological and hormonal parameters in thyroid lesions, and thus TFTs are not very helpful on their own [14]. In equivocal cases antibody testing is helpful, but about 7 to 33% cases of HT are antibody negative. This can be explained; as localized immune destruction occurs much earlier before serological findings. In this way, cytological evidence is more superior than hormonal and serological findings [14, 20].

There were a few limitations in our study. Firstly, all cases of FNAC did not have biochemical parameters for correlation. Secondly, as the tests are costly, the patients were not able to undergo all the diagnostic tests. Thirdly, the number of cases were limited as most of

ISSN 2515-8260 Volume 09, Issue 06, 2022

the lesions did not necessitate surgical intervention.

Conclusion

This study reaffirms that cytology still remains the gold standard for the diagnosis of thyroid lesions. Hormonal status alone does not help in screening of thyroid lesion. Accurate sampling and USG guided FNAC for sub-centimeter size nodules can help in reducing the number of indeterminate, false-positive, and false-negative diagnoses. In cytologically equivocal cases combination of cyto-morphology, clinical features, thyroid hormonal profile, antibody testing and ultra-sonographic features help in the diagnosis of thyroid lesions. It is recommended that surgical indications must not depend solely on cytology. Indeed, the results of medical history, physical examination, laboratory tests and ultrasonography should also be evaluated simultaneously. Further studies correlating the FNAC results and surgical confirmation can help in strengthening the evidence in support of cytological diagnosis.

Source of funding

No financial support was received for the work within this manuscript.

Conflict of interest

The authors declare they have no conflict of interest.

Table 1: Distribution of cases according to The Bethesda System for Reporting Thyroid Cytology (TBSRTC) (n = 186)

Category	Cytological diagnosis	No. of Cases	Percentage
I	**Non-diagnostic or Unsatisfactory**	6	3.2%
II	**Benign** Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.).	121	65.1%
	Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context.	39	20.9%
	Consistent with granulomatous (subacute) thyroiditis.	3	1.6%
III	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance.	8	4.3%
IV	Follicular Neoplasm or Suspicious for a Follicular Neoplasm.	3	1.6%
V	Suspicious for Malignancy.	4	2.2%
VI	Malignant.		
	Papillary carcinoma of thyroid.	2	1.1%
	Total	186	100%

Table 2: Correlation of Thyroid function test with Bethesda categories (n = 118)

TFT	TBSRTC categories					
	I	II	III	IV	V	VI
Euthyroid	2	58	7	1	2	0
Hyperthyroid	2	19	0	0	0	0
Hypothyroid	0	25	0	1	0	1
Total	4	102	7	2	2	1

Table 3: Comparison of Distribution of Cases of Various Studies According to TBSRTC

Study	I(%)	II(%)	III(%)	IV(%)	V(%)	VI(%)
Present study	3.2%	87.6%	4.3%	1.6%	2.2%	1.1%
Mehra P *et al*.	7.2	80	4.9	2.2	3.6	2.2

ISSN 2515-8260 Volume 09, Issue 06, 2022

Reddy G L *et al*.	6	66	4	6	2	6
Thakor T *et al*.	6.4	80	2.4	4.0	4.0	3.2
Jain V *et al*.	10.9	69.1	1.8	10.9	1.2	6.1
Mondal KS *et al*.	1.2	87.5	1	4.2	1.4	4.7

Table 4: Comparison of thyroid function test of various studies in lymphocytic thyroiditis

Studies	**Hormonal status**			**Total**
	Euthyroid	**Hypothyroid**	**Hyperthyroid**	
Present study	10(34.5%)	14 (48.3%)	5(17.2%)	39
Megalamane S *et al*.	49 (50%)	43(43.9%)	6 (6.1%)	98
Gupta C *et al*.	21(26.92%)	42(53.85%)	15(19.23%)	78
Iha *et al*.	5 (16.20%)	17(54.80%)	9 (29.0%)	31
Monda R *et al*.	10(8.8%)	67 (59.3%)	36(31.9%)	113

References

1. Reddy GL, Begum Z, Patil A. Bethesda reporting of thyroid FNACS with T3, T4, TSH correlation in a medical college of North Karnataka. IP J Diagn Pathol Oncol 2020;5(4):405-409.
2. Layfield LJ. Atlas of fine needle aspiration cytology, 1st edition, 2014, 40-41.
3. Orell SR, Sterrett GF. Orell & Sterrett's Fine Needle Aspiration Cytology. 5th ed. New Delhi: RELX India Private Limited., 2012.
4. Mehra P, Verma AK. Thyroid cytopathology reporting by the Bethesda system: A two year prospective study in an academic institution. Pathology research international, 2015. Article id 240505: 1-11.
5. Ali SZ, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria and Explanatory Notes. 2nd ed. Switzerland: Springer, 2018.
6. Carl A Burtis, Edward R Ashwood, David E Bruns. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th Eddition. Philadelphia: WB Sounders, 2012, 21-70.
7. Bhatta S, Makaju R, Mohammad A. Role of fine needle aspiration cytology in the diagnosis of thyroid lesions. Journal of Pathology of Nepal. 2012;2:186-188.
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov Y, *et al*. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016 Jan;26(1):1-133. Doi: 10.1089/thy.2015.0020. PMID: 26462967; PMCID: PMC4739132.
9. Thakor T, Daveshwar MR, Shah HS. Cyto-morphological study of thyroid lesions using the Bethesda system for reporting thyroid cytology and its correlation with Thyroid Function Test. J Evolution Med. Dent. Sci. 2020;9(12):949-952. DOI: 10.14260/jemds/2020/204.
10. Jain V, Agrawal V, Kalra R, Tripathi SK. Study of cytomorphological features of thyroid lesions and its correlation with thyroid function tests. Medica Innovatica. 2021;10(2):55-59.
11. Das MK, Basnet M. Cytological Evaluation of Thyroid and its Correlation with Thyroid Function Test and Anti-Thyroid Peroxidase in a Patient of Hashimoto's Thyroiditis, JoNMC. 2019;8(2)57-61.
12. Mondal KS, Sinha S, Basak B, Roy DN, Sinha SK. The Bethesda system for reporting thyroid fine needle aspirates: A cytologic study with histologic follow up. 2013;30(2):94-99.

13. Megalamane S, Anantharamaiah H, Kurpad SN. Correlation of Cytological Grading in Lymphocytic Thyroiditis with Thyroid Hormones and Antibodies-A Retrospective Study in the Era of Bethesda System of Thyroid Reporting. Journal of Clinical and Diagnostic Research. 2018 Aug;12(8):EC01-EC044.
14. Gupta C, Bhardwaj S, Sharma S. Cytological grading of lymphocytic thyroiditis and its correlation with thyroid hormonal status. Indian J Pathol Oncol. 2020;7(3):369-373.
15. Iha, Bhardwaj A, Kumar R, Acharya S. Cytomorphic Study of Lymphocytic Thyroiditis: A Correlation between Cytological Grade and Biochemical Parameters. Journal of Clinical and Diagnostic Research. 2019 Jun;13(6):EC05-EC09.
16. Monda R, BiPlaB KuMaR Biswas BK, Phalguni Chakrabarti P, Mandal P. Fine Needle Aspiration Cytology of Thyroid Lesions in a Tertiary Care Hospital Catering Predominantly the Tribal Population: Special Reference to Autoimmune Thyroiditis. National Journal of Laboratory Medicine. 2021 Jul;10(3):PO34-PO37.
17. Chandanwale SS, Nair R, Gambhir A, Kaur S, Pandey A, Shetty A, *et al*. Cytomorphological Spectrum of Thyroiditis: A Review of 110 Cases. Hindawi Journal of thyroid Research, 2018, 7. Article ID 5246516, https://doi.org/10.1155/2018/5246516.
18. Shetty A, Chowdappa V. Cytomorphological spectrum of Hashimoto's thyroiditis and its correlation with hormonal profile and hematological parameters. J Cytol. 2019;36:137-41.
19. Anand A, Singh KR, Kushwaha JK, Hussain N, Sonkar AA. Papillary Thyroid Cancer and Hashimoto's Thyroiditis: An Association Less Understood. Indian J Surg Oncol. 2014 Sep;5(3):199-204.
20. Sahoo N, Naik S, Mohanty P, Sahoo PN, Das P. The cytomorphological spectrum of Hashimoto thyroiditis and its correlation with serological parameters: A study in the coastal region. J NTR Univ Health Sci., 2020;9:25.