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Original Article

Pathology Section

Lymphocytic Thyroiditis- Association between Cytology and Biochemical Findings

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ABSTRACT

Introduction: Hashimoto's thyroiditis otherwise called as chronic lymphocytic thyroiditis is the most common cause of hypothyroidism and one of the most common thyroid lesions in Fine Needle Aspiration Cytology (FNAC). Diagnosis depends on clinical findings, ultrasonographic findings, thyroid profile and antithyroid antibody levels along with the FNAC findings. Not much studies are there which have assessed the association of the clinical and biochemical parameters with the cytological findings.

Aim: To grade the cytological features of lymphocytic thyroiditis and to study the association of the grades with Thyroid Function Test (TFT) and antithyroid antibody levels.

Materials and Methods: A prospective time bound analytical observational study of one year was carried out in the Department of Pathology at Government Medical College, Palakkad, Kerala, India after obtaining approval from the Institutional Ethics Committee (IEC). Out of the total of 462 cases of thyroid lesions who underwent Fine Needle Aspiration (FNA), 147 cases were lymphocytic thyroiditis as per cytology. Of these, 40 cases had Thyroid Stimulating Hormone (TSH), Antithyroglobulin Antibody (ATG) and Antithyroid Peroxidase Antibody (ATPO) levels known which were included in the study. Cytological grading of those were done and the association of the same with the above mentioned parameters was studied. Data was analysed using Statistical Package for the Social Sciences (SPSS) software. Descriptive statistics were calculated and presented as percentages, mean and Standard Deviation (SD). Chi-square test was used to find the association between the categorical variables. The p-value <0.05 was taken as statistically significant.

Results: Cytomorphology was diagnostic of thyroiditis in all the cases. Out of the 40 cases, 32 were females.The most common age group affected was 31-40 years, though it ranged from 18-68 years. Most common clinical presentation was diffusely enlarged thyroid, though a few presented as nodular disease. Most of the patients had grade 1 thyroiditis (23 cases) followed by grade 2 (13 cases). Elevated antithyroid antibody levels - ATPO elevated in 32 cases and ATG in 20 cases. TSH was seen elevated in 28 cases of thyroiditis. No association was observed with the antithyroid antibody levels and the cytological grade.

Conclusion: Lymphocytic infiltration into the follicles is the diagnostic cytological feature of chronic lymphocytic thyroiditis. TSH elevation and positive ATPO levels strongly suggest Hashimoto's thyroiditis. No association was found between the cytological grade and TSH and antibody levels.

Keywords: Autoimmune thyroiditis, Cytological grade, Fine needle aspiration, Hashimoto's thyroiditis, Hypothyroidism, Thyroid antibodies, Thyroid function tests, Thyroid stimulating hormone

INTRODUCTION

Hashimoto's thyroiditis synonymously known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis, first described by Hakaru Hashimoto in 1912 is an autoimmune disease which is the most common cause of hypothyroidism in developed countries, while inadequate iodine intake is the cause worldwide [1]. It is the second most common thyroid lesion next to goitre [2]. The pathophysiology of the disease is due to the formation of antithyroid antibodies and the follicular cells are destroyed by cell and antibody mediated pathways leading to fibrosis. The diagnosis is challenging and in most of the times, clinical features, biochemical parameters, ultrasound findings and cytological features are together needed to arrive at a diagnosis. The diagnostic cytological feature in Hashimoto's thyroiditis include infiltration of follicular cell clusters by lymphocytes and transformed forms, presence of Hurthle cells, follicular cells showing anisonucleosis and occasional presence of epithelioid cells and giant cells [2-4].

Not much studies are available in our population which investigated the association of cytological grades of lymphocytic thyroiditis with clinical features and biochemical findings. The aim of the present study was to assess the cytological grade following the criteria of Bhatia A et al., [4] and to study the association of cytological grades with ATPO, ATG and TSH levels.

MATERIALS AND METHODS

A prospective time bound analytical observational study of one year (from December 2019-December 2020) was carried out in the Department of Pathology at Government Medical College, Palakkad, Kerala, India, after obtaining approval from the Institutional Ethics Committee (IEC) ID-GMC/IEC/23. During the study period a total of 462 cases of thyroid swellings were referred to our department for FNA and samples were obtained after getting informed consent.

Inclusion criteria: All the cases of lymphocytic thyroiditis were included in the study. The relevant clinical details, radiological and biochemical findings were recorded in prescribed proforma.

Exclusion criteria: Those patients with no TSH, ATPO and ATG values available were excluded from the study. Out of the 147 cases of lymphocytic thyroiditis, only 40 cases had TSH, ATPO and ATG levels available.

Both aspirational and non aspirational techniques were used to obtain adequate sample. Maximum of 2-4 passes were done on a single prick using a 23 G needle. The smears were fixed in 80% isopropyl alcohol and stained by Papanicolaou stain. Air dried smears were also studied with Giemsa stain. In case, if the material obtained was not satisfactory, a repeat aspiration was tried. The cytological diagnosis of lymphocytic thyroiditis was based on presence of lymphocytic infiltration into the follicular cell clusters, presence of lymphocytes, transformed forms and plasma cells, epithelioid cells and giant cells, presence of Hurthle cells and anisonucleosis in follicular cells. Cytological grading was done according to Bhatia A et al., [4] [Table/Fig-1] based on the extent of lymphocytic infiltration, presence of lymphoid follicles and germinal centre, Hurthle cell

change and presence of epithelioid cells. Reference range for TSH was 0.27-5.5 IU/mL, ATPO and ATG being <35 IU/mL. Cytological grading was done so in 40 cases and the association of those grades with raised or normal TSH, ATPO and ATG levels was assessed.

Grade 0	No lymphoid cells
Grade 1	Few lymphoid cells infiltrating the follicles/increased number of lymphocytes in the background
Grade 2	Moderate lymphocytic infiltration or mild lymphocytic infiltration with Hurthle cell change/giant cells/ anisonucleosis
Grade 3	Florid lymphocytic inflammation with germinal centre formation, very few follicular cells left

[Table/Fig-1]: Cytological grading by Bhatia A et al., [4].

STATISTICAL ANALYSIS

Data was analysed using SPSS version 20.0. Descriptive statistics were calculated and presented as percentages and mean±SD. Chi-square test was used to find the association between the categorical variables. A p-value <0.05 was taken as significant.

RESULTS

Forty cases of lymphocytic thyroiditis were studied, females were the most commonly affected, 32 cases (80%). Most common age group affected was 31-40 years, 16 cases (40%) followed by 51-60 years, 7 cases (17.5%). Six cases each were found in age groups 21-30 years and 41-50 years (15% each). Four cases (10%) were found in >60 years while only a single case was found in ≤20 years (2.5%). Thirty three (82.5%) patients presented as diffuse enlargement of thyroid while 6 patients (15%) had nodular disease [Table/Fig-2]. TSH was elevated in 28 (70%) cases and was normal in 12 (30%) cases [Table/Fig-3]. ATPO was elevated in 32 (80%) cases and normal in 8 (20%) cases [Table/Fig-4]. ATG was elevated in 20 (50%) cases and was normal in 20 (50%) cases [Table/Fig-5].

Nature of the swelling	Grade n (%)				p-value
	1	2	3	Total	
Diffuse	21 (63.6%)	8 (24.2%)	4 (12.1%)	33	0.16
No swelling	0	1 (100%)	0	1	
Nodule	2 (33.3%)	4 (66.7%)	0	6	

[Table/Fig-2]: Comparison of clinical presentation with grade.

TSH	Grade n (%)				p-value
	1	2	3	Total	
High	16 (57.1%)	9 (32.1%)	3 (10.8%)	28	0.974
Normal	7 (58.3%)	4 (33.3%)	1 (8.4%)	12	

[Table/Fig-3]: Comparison of TSH with grade.

ATPO	Grade n (%)				p-value
	1	2	3	Total	
High	21 (65.6%)	9 (28.1%)	2 (6.3%)	32	0.081
Normal	2 (25%)	4 (50%)	2 (25%)	8	

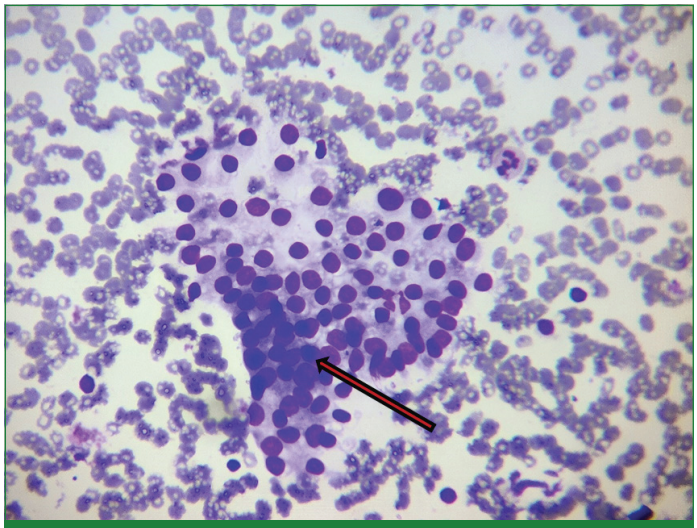
[Table/Fig-4]: Comparison of ATPO with grade.

ATG	Grade n (%)				p-value
	1	2	3	Total	
High	12 (60%)	7 (35%)	1 (5%)	20	0.571
Normal	11 (55%)	6 (30%)	3 (15%)	20	

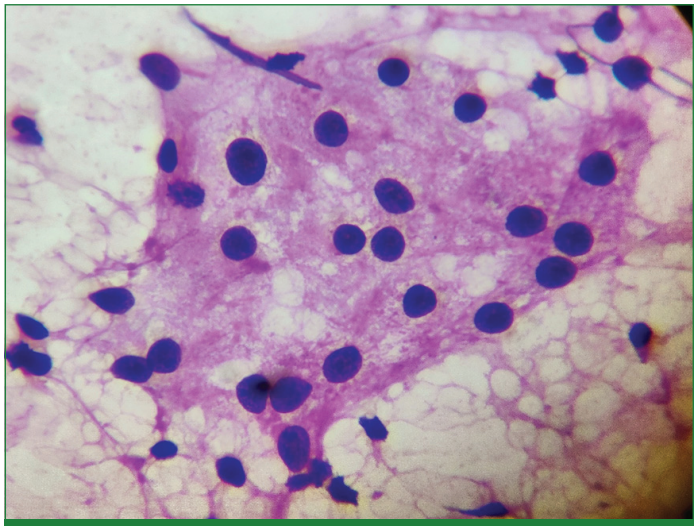
[Table/Fig-5]: Comparison of ATG with grade.

According to Bhatia A et al., grade 1/mild disease was characterised by a few lymphoid cells infiltrating the follicles/increased number of lymphocytes in the background [Table/Fig-6]. Grade 2/moderate disease showed moderate lymphocytic infiltration with Hurthle cell change, anisonucleosis and giant cells [Table/Fig-7] and grade 3/severe disease showed florid lymphocytic infiltration with germinal centre formation [Table/Fig-8] [4]. In present study, it was found that 23 cases (57.5%) had grade 1 thyroiditis and 13 cases (32.5%) had grade 2 thyroiditis. Only 4 cases (10 %) had grade 3 thyroiditis. The association of these grades was assessed with the TSH, ATPO and ATG levels (if high or normal) and the p-value was found to be >0.05. Gender based comparison of TSH, ATPO and ATG also showed no significant association [Table/Fig-9].

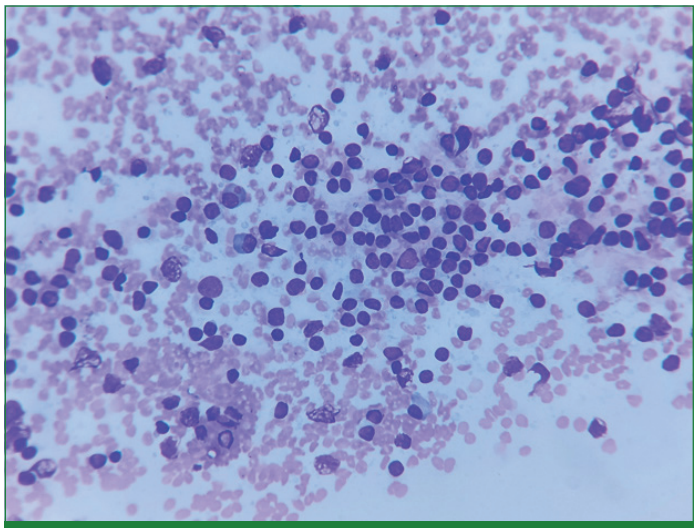
Lymphocytic infiltration into the follicles as well as lymphocytes in the background were found in all 40 cases (100%) while Hurthle cell



[Table/Fig-6]: Lymphocytes infiltrating the follicles (Giemsa x100).



[Table/Fig-7]: Hurthle cells and follicular cells showing anisonucleosis (Pap smear x1000).

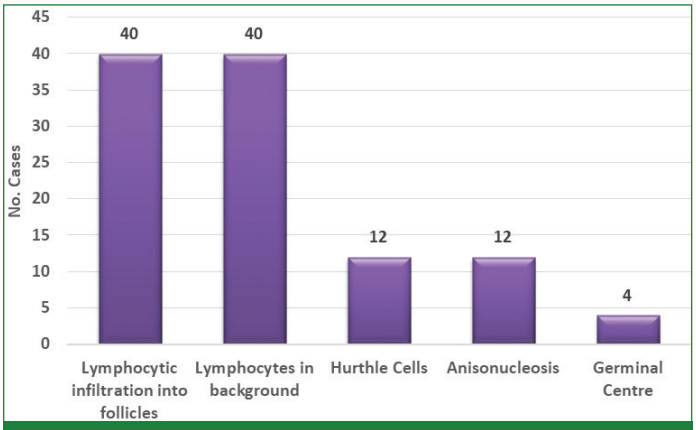


[Table/Fig-8]: Germinal centre cells- centroblasts, centrocytes and plasma cells with no follicular cells (Giemsa x400).

change and anisonucleosis in the follicular cells were found in 12 cases (30%) as shown in [Table/Fig-10].

Variable	Group	Gender		p-value
		Male n (%)	Female n (%)	
TSH	High	6 (21.43%)	22 (78.57%)	0.73
	Normal	2(16.67%)	10 (84.33%)	
ATPO	High	7 (21.88%)	25 (78.12%)	0.553
	Normal	1 (12.5%)	7 (87.5%)	
ATG	High	4 (20%)	16 (80%)	1
	Normal	4 (20%)	16 (80%)	

[Table/Fig-9]: Comparison of TSH, ATPO and ATG levels among males and females.



[Table/Fig-10]: Cytological features of lymphocytic thyroiditis.

DISCUSSION

Hashimoto's thyroiditis or chronic lymphocytic thyroiditis is an autoimmune inflammation of thyroid gland where there is antibody mediated destruction of thyroid follicles and lymphocytic infiltration. Clinically characterised by an initial phase of hyperthyroidism due to the release of thyroid hormones as a result of thyroid damage followed by hypothyroidism because of the minimal atrophied thyroid follicles and extensive fibrosis [1,4]. Depending upon the stage of disease, the clinical features, thyroid hormone levels and antithyroid antibody levels vary.

In the present study, the association of cytological grades of lymphocytic thyroiditis with TSH, ATPO and ATG levels was assessed as suggested by Bhatia A et al., [4] with a detailed analysis of all the data of the patients included in the study.

Most of the patients were females (80%), which was in concordance with the data in most of the literatures [1,4-6] [Table/Fig-11]. The increased incidence in females may be attributed to the X-chromosome which has genes related to preservation of immune tolerance [7,8]. Though the cases ranging from 18 to 68 years were seen, most of the patients affected were from 3rd and 4th decade as mentioned in previous studies [1,4]. Most of the patients had diffusely enlarged thyroid as described classically about Hashimoto's thyroiditis with only 15% patients presenting as nodular disease in concordance with the previous studies [1,4,6]. There was no association with this clinical presentation and grade of thyroiditis. Though Hashimoto's thyroiditis can present as a nodular disease [9]. The main differential will be a neoplasm for which combined approach is needed to rule out with radiology, biochemical parameters like TSH, ATPO and ATG levels and cytology findings, FNA being highly sensitive in diagnosing Hashimoto's thyroiditis with a diagnostic accuracy rate of 92% [1,2]. In the present study, all the cases of thyroiditis with nodular disease had co-existent colloid goitre which explained the nodular clinical presentation as in Chandanwale SS et al., where the most common associated lesion with Hashimoto's thyroiditis was colloid goitre [7]. Raised ATPO was seen in 80% cases in concordance with the earlier studies which also showed that the most common antibody associated with Hashimoto's thyroiditis is ATPO followed by ATG [1,10,11]. About 50% patients showed raised ATG levels in the current study which goes in concordance with the studies earlier [1,12,13].

Author	No. of cases	Age	Sex	Swelling diffuse	Swelling nodular	Grade	Association of grade with biochemical parameters
Bhatia A et al., [4]	76	6-60 years MC 30-40 years	F 70 M 6	89.47%	2.63%	1-38.67% 2-44% 3-17.33%	No association
Kumar N et al., [6]	55	7-45 years MC <30 years	F 55	81.8%	18.2%	1-61.90% 2 and 3-38.16%	No association
Sood N and Nigam JS [5]	55	MC 21-30 years	F 50 M 5	-	-	1-21.82% 2-30.9% 3-47.27 %	Grade 3 has association with raised TPO and TSH Rest no association
Anila KR et al., [1]	60	MC 31-40 years	F 55 M 5	77%	14%	1-45 % 2-36.67% 3-18.33%	No association
Present study	40	MC 31-40 years	F 32 M 8	82.5%	15%	1-57.5% 2-32.5% 3-10%	No association

[Table/Fig-11]: Lymphocytic thyroiditis-Comparison with previous studies [1,4-6].
MC: Most common; F: Female; M: Male

Cytological grading was done according to Bhatia A et al., as shown in [Table/Fig-1] [4]. Majority had grade 1 thyroiditis which was in concordance with a few earlier studies [1,3,6], while in many other studies it was grade 2 thyroiditis which was seen commonly [4,8,11,14]. The present study failed to show any statistical association between the cytological grade and biochemical findings which goes along with most of the previous studies [1,4,6,13,14]. Balanced distribution of hypothyroid cases was noted in all grades [10,13]. Most common cytomorphological feature in all cases of thyroiditis was lymphocytic infiltration into the follicles and in the background similar to what was observed in previous studies [4,10,15]. Though none of these features were statistically significant, those findings in FNA will help us in raising a suspicion of lymphocytic thyroiditis especially in a low yield aspirate.

Limitation(s)

Since the measurement of antithyroid antibodies could be conducted only in a limited number of participants due to financial and logical considerations, the results of the present study may not be exactly representative of the study population.

CONCLUSION(S)

Though the diagnosis of Hashimoto's thyroiditis is a collective one based on cytology, radiology and biochemical parameters, the gold standard for definitive diagnosis still is lymphocytic infiltration into the follicular cell clusters demonstrated by FNA. Hashimoto's thyroiditis is strongly associated with elevated antithyroid antibody levels especially ATPO. In accordance with the previous studies, the present study too couldn't find any relationship with the cytological grade and TSH, ATPO and ATG levels.

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