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Lymphocytic Thyroiditis: A Correlation Between Cytological Grading and Thyroid Function Tests

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***Abstract*---**Sixty five cases of chronic lymphocytic thyroiditis were included in the study. Most of the study subjects were females [61 cases (94%)] and male to female ratio was 1:15. The most common age group was? 40 years (52 cases, 80%). Grade I lymphocytic thyroiditis was observed in seventeen (17 cases, 26%) cases, Grade II in twenty eight cases (28 cases, 43.07%) and Grade III thyroiditis was seen in twenty (20 cases, 31%) cases. Anti-TPO and TSH values were increased in 95% (19/20) of cases with grade 3 lymphoid infiltrate, 92.8% (26/28) of cases with grade 2, and 94.1% (16/17) of cases with grade 1. The diagnosis of Hashimoto Thyroiditis should be based on a multidisciplinary approach wherein clinical, radiological, biochemical, cytological, and radionuclide parameters are taken into consideration. However, in spite of the availability of different diagnostic modalities, demonstration of lymphocytic infiltration on cytologic smears still remains the gold standard.

***Keywords*---**cytological grading, fine needle aspiration (FNA), hashimoto's thyroiditis, lymphocytic thyroiditis, thyroid function.

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Introduction

Lymphocytic thyroiditis (struma lymphomatosa) was first described by Hakaru Hashimoto in 1912, which has his name (Uma et al., 2013). Chronic lymphocytic thyroiditis also known as Hashimoto's thyroiditis or autoimmune thyroiditis, is the second most common thyroid lesion diagnosed on FNAC after goiter. It is one of the important causes of goiter and hypothyroidism. Hurthle cell change and an increased number of mature and transformed lymphocytes impinging on follicular cells is the characteristic of Hashimoto's thyroiditis. The disease is characterized clinically by an active phase which is transient exhibiting clinical manifestations of hyperthyroidism followed by evolution and destructive phase that manifest with subclinical or overt hypothyroidism (Bhatia et al., 2007).

Although, the most common cause of hypothyroidism is iodine deficiency worldwide, but the commonest cause of spontaneous hypothyroidism in areas of adequate iodine intake remains lymphocytic thyroiditis. The annual incidence of lymphocytic thyroiditis worldwide is estimated to be 0.3-1.5 cases per 1000 persons exhibiting a female predilection, with peak incidence occurring in 30-50 years of age (Pradhan et al., 2016). Cytological grading on FNAC smears using predefined sets of criteria was for the first time done by Bhatia et al. who tried to correlate the lymphoid density with clinical, radiological, and biochemical parameters (Bhatia et al., 2007). The smears diagnosed as lymphocytic thyroiditis were graded into three grades (Grade 1,2,3). Thyroid dysfunction can be assessed by measuring serum TSH, T4 and T3 levels, but significant changes in their levels are seen late in the disease process. Several studies have reported that on ultrasonography, reduction in thyroid echogenicity occurs at a relatively early stage in the autoimmune thyroiditis, often before overt thyroid failure, and is a strong indicator of autoimmune process even when these disorders have not been suspected clinically (Uma et al., 2013).

Even though several tests for diagnosis of chronic lymphocytic thyroiditis are available, Fine Needle Aspiration Cytology (FNAC) remains the gold standard. Fine needle aspiration cytology (FNAC) is a highly sensitive measure in diagnosing Hashimoto's (lymphocytic) thyroiditis, with a diagnostic accuracy rate of 92% (Kocjan, 2006). The diagnosis of the disease on fine needle aspiration cytology (FNAC) smears is made by finding the oxyphilic transformation of follicular epithelial cells (Hurthle cells), infiltration of follicles by lymphocytes and plasma cells, presence of moderate number of lymphoid cells in background with scanty or absent colloid in the background (Orell et al., 2005). The present study aims to correlate Fine Needle Aspiration(FNA) cytologic findings with Thyroid function tests in lymphocytic thyroiditis.

Materials and Method

This is a retrospective study conducted in the Department of Pathology, GMC Jammu over a period of one year from July 2019 to June 2020. Out of 256 thyroid aspirations done during the study period, 65 cases of chronic lymphocytic thyroiditis were diagnosed on cytology which were included in the study for which biochemical parameters were available. Old cases of lymphocytic thyroiditis already on medication and those with any other additional lesion observed along

with lymphocytic thyroiditis diagnosed on cytology are excluded from the study. The relevant clinical details of the patient were noted. Thyroid function tests were used to evaluate blood concentrations of thyroid hormones. The patients had estimation of T3, T4 & TSH. The reference range used was T4 (55 – 135 ng/ml), T3(0.7 – 2ng/ml) and TSH(0.17 – 4.05 µIU/ml) (Uma et al., 2013). Depending on these results patients were considered euthyroid, hyperthyroid, and hypothyroid.

FNA of thyroid gland was done both by aspiration and non-aspiration technique whichever obtained the material better. Qualitative criteria used for cytologic diagnosis were lymphocytes and plasma cells infiltrating the thyroid follicles and increased number of lymphocytes in the background with or without lymphoid follicles, Hurthle cell change, multinucleated giant cells, epithelioid cell clusters, anisonucleosis or interlobular fibrosis can also be seen. Quantitation of chronic lymphocytic thyroiditis was done by a cytological grading system based on number of lymphocytes infiltrating the gland, the degree of destruction caused (relative proportion of inflammatory and follicular epithelial cells) and presence of associated features like Hurthle cell change, giant cells, anisonucleosis etc. The smears with diagnosis of chronic lymphocytic thyroiditis were graded into three grades by adopting Bhatia et al grading system on cytology (Bhatia et al., 2007).

- Grade I [Mild]: Few lymphoid cells infiltrating the follicles/increased number of lymphocytes in the background
- Grade II [Moderate]: Moderate lymphocytic infiltration or mild lymphocytic infiltration with Hurthle cell change/giant cells/anisonucleosis
- Grade III [Severe]: Florid lymphocytic inflammation with germinal centre formation, very few follicular cells left.

Results

Sixty five cases of chronic lymphocytic thyroiditis were included in the study. Most of the study subjects were females [61 cases (94%)] and male to female ratio was 1:15. The most common age group was ≤ 40 years (52 cases, 80%).

Table 1
Age and sex distribution of study subjects

		SEX				
		FEMALE		MALES		TOTAL
		No.	%	No.	%	
AGE GROUP	≤40 years	50	96.1	2	3.84	52
	41-60 years	9	90	1	10	10
	>60 years	2	66.6	1	33.3	3
TOTAL		61	94	4	6	65

The cytologic features in these cases showed lymphocytic infiltration of the thyroid follicular cells and lymphocytes in the background. Lymphocytic thyroiditis was reevaluated according to the criteria set by Bhatia et al. from grade 1 to grade 3 and were correlated with anti-TPO and hypersensitive TSH. Grade I lymphocytic thyroiditis was observed in seventeen (17 cases, 26%) cases and showed mild lymphocytic infiltration of follicular epithelial cells, Hurthle cell

change, and giant cells. Grade II was observed in twenty eight cases (28 cases, 43.07%) and characterized by moderate amount of lymphocytic infiltrate with evidence of follicular destruction, Hurthle cell change, giant cells. Grade III thyroiditis was seen in twenty (20 cases, 31%) cases and characterized by dense lymphoid infiltrates with germinal centers and with few residual follicular cells, Hurthle cell change, giant cells, and granulomas. Lymphoid infiltrate consists of polymorphous population of lymphoid cells consisting of mature lymphocytes, centrocytes, centroblast, and plasma cells.

Table 2
Cytological grading of cases of lymphocytic thyroiditis – 65 cases

Grades of chronic Lymphocytic Thyroiditis	No. of cases	Percentage (%)
I	17	26
II	28	43
III	20	31
Total	65	100

Anti-TPO and TSH values were increased in 95% (19/20) of cases with grade 3 lymphoid infiltrate, 92.8% (26/28) of cases with grade 2, and 94.1% (16/17) of cases with grade 1. Statistical correlation of grades of thyroiditis was carried out between them by using SPSS 20 version. (Table 3).

Table 3
Grading of lymphocytic thyroiditis and anti-TPO and TSH relation

	Lymphocytic Grade			Total
	1+	2+	3+	
Anti-TPO increase TSH increase	5	21	16	42
Anti-TPO increase TSH normal	6	3	2	11
Anti-TPO increase TSH low	5	2	1	8
Anti-TPO normal TSH increase	1	2	1	4
Total	17	28	20	65

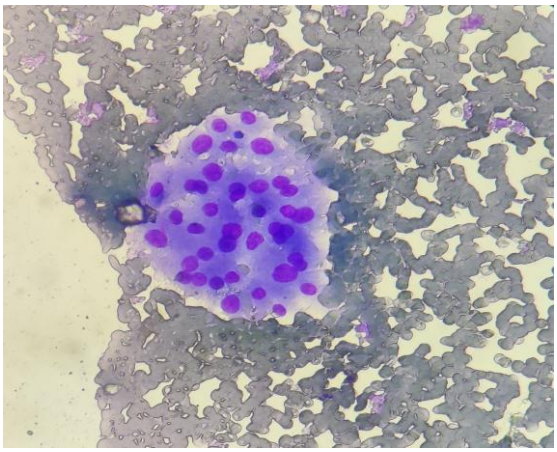

Figure 1. *Grade I*- cluster of follicular epithelial cells infiltrated by few lymphoid cells (MGG, 40X)

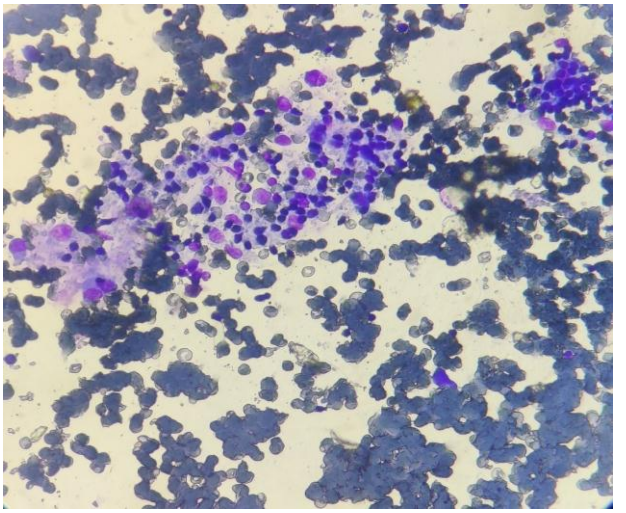

Figure 2. *Grade II* – cluster of follicular epithelial cells showing moderate lymphocytic infiltration (MGG, 40X)

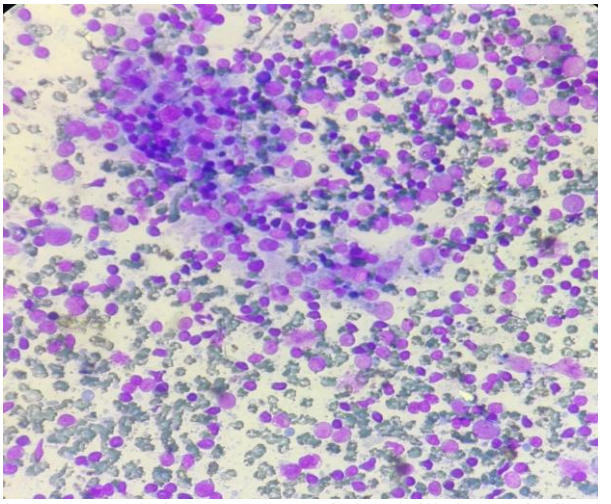

Figure 3. *Grade III* – total destruction of the follicle with florid lymphocytic infiltration (MGG, 40X)

Discussion

Hashimoto's thyroiditis is also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis including atrophic and non-goitrous thyroiditis (Amino et al., 1999). It is an autoimmune disease which is characterized by activation of CD4+T cells which further initiate the recruitment of auto-reactive B cells and thus produce a variety of thyroid autoantibodies. Presence of autoantibodies Thyroid peroxidase (TPO) and Thyroglobulin (Tg) in the patient's sera, against two major thyroid antigens is the principal biochemical characteristic of the disease (Weetman & McGregor, 1994; Dayan & Daniels, 1996).

Chronic lymphocytic thyroiditis can affect any age group, but in the present study, the commonest age group of presentation was less than 40 years which is in concordance with other studies, who have opined that the disease most commonly affects patients in 21-30 years of age group. Bhatia et al. observed the most common age group to be the 3rd to 4th decade (Bhatia et al., 2007). According to a study by Sood & Nigam (2014), the commonest age group of presentation was 21-30 years (Sood & Nigam, 2014). In another study by Iha et al. the commonest age group was below 40 years which is in concordance with our study (Bhardwaj et al., 2019). The occurrence of disease in younger age group is due to deficiency of iodine in non coastal areas which is still prevalent despite of national iodine deficiency diseases control program. In elderly people, the disease may be seen in iodine sufficient areas. Many authors have linked increased incidence of HT particularly in coastal areas due to excess intake of iodine (Uma et al., 2013; Kumar et al., 2002).

In the present study female predominance was noted which is similar to the observations by other authors who have noticed a female predilection for the disease in their studies. The occurrence of disease in females has a early onset while in males it usually presents at a late age group (Uma et al., 2013; Sood & Nigam, 2014; Bhardwaj et al., 2019; Kumar et al., 2002). In the present study, the most common clinical presentation was diffuse thyroid swelling which was seen in fifty two patients (80%) while thirteen patients (20%) presented with nodular disease of the thyroid. This is comparable with the observations made (Bhardwaj et al., 2019). But this observation is significantly higher in comparison to a study done by Bhatia A et al., in which only 2.63% of patients presented with nodular disease (Bhatia et al., 2007). The authors have the opinion that nodular disease usually represents the early stages of Hashimoto's (lymphocytic) thyroiditis. But the patient usually reports to the physician in the advance stage of the disease, where the clinical and hormonal changes have already been established and patient clinically presents with diffuse thyroid swelling (Singh et al., 2009). This is supported by our observation that in the present study a normal TSH values was observed in 5 cases (16.12%) while Anti-TPO value was raised in 26 cases (83.87%) and nodular disease was observed in four cases (12.9%). In hashimoto's thyroiditis autoantibodies cause destruction of thyrocytes which leads to abnormalities in the hormonal levels. Therefore, in the early stages, the autoantibodies are raised with normal hormonal values. Later on, the hormonal abnormalities also set in.

Majority of the patients presented with clinical features of hypothyroidism i.e. weight gain (40.7%), hypothermia (38.9%) and fatigue/lethargy (39.7%). On hormonal assay, forty six (70.70%) patients showed hypothyroidism, suggesting an advanced stage of the disease at the time of diagnosis and represented destructive phase of the disease. There were eight cases of hyperthyroidism (12.3%) 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, eleven cases were euthyroid (16.9%) with normal levels of T3 and T4 indicating disease in phase of evolution. This is similar to and correlate with studies by Bhardwaj et al. (2019); Kumar et al. (2002); Singh et al. (2009), in which most of the patients were hypothyroid (Bhardwaj et al., 2019; Kumar et al., 2002; Singh et al., 2009).

On cytologic examination of the thyroid aspirate smears, it showed L: E ratio (lymphoid: epithelial ratio) in Hashimoto's thyroiditis ranging from 2:1 to 10:1 (Kumar et al., 2002). In our study, all the 65 cases (100%) showed lymphocytes in the background with infiltration into the thyroid follicular cells. Other features that were observed were anisokaryosis, hurthle cell change, giant cells, epitheliod like cells, plasma cells and germinal centre formation. On subjecting these cases to cytological grading, it was observed that, seventeen (27%) patients were of grade-I thyroiditis on cytology. The aspirate smears of these patients showed the presence of increased number of lymphocytes in the background or the lymphoid cells were noted to infiltrate thyroid follicular cells. Grade II thyroiditis was seen in Smears of twenty eight patients (43%), the cytologic features observed were presence of Hurthle cells, epithelioid cells, giant cells, anisonucleosis and increased number of lymphocytes. Twenty cases (31%) of grade-III thyroiditis showed presence of florid lymphocytic infiltration with germinal center formation with the presence of scanty follicular cells. In our study, most of the patients presented with grade-II disease which is supported by the studies done (Bhatia et al., 2007; Bhardwaj et al., 2019). However, in the study by Anila et al. (2016), maximum number of the patients presented with grade-I disease (Singh et al., 2009).

The present study showed elevated anti-thyroid peroxidase antibody (Anti-TPO) values in sixty one cases (93.8%), all of these patients showed characteristic cytological features of lymphocytic thyroiditis on smears. Detection of autoantibodies against Tg and TPO antigens are clinically most important for diagnosis and are found to be elevated in up to 95% of the patients [6]. However, it is debatable to establish a diagnosis of the disease solely based on raised anti TPO. Anti-TPO positivity correlates strongly with the cytological diagnosis of lymphocytic thyroiditis (p-value=0.001 to 0.05) but its values do not correlate with the severity of disease. In a study done by Guarda LA and Baskin HJ, the antibody positive cases were found to be morphologically indistinguishable from the seronegative cases (Guarda & Baskin, 1987). It is an established fact and can be observed from studies done by other authors that localized intrathyroidal immune destruction begins at a much earlier stage than serologic evidence of disease. Thus, antibody titers may vary in the course of disease but cytomorphologic features persist during the course of lymphocytic thyroiditis.

Conclusion

To conclude we are of the opinion that the diagnosis of Hashimoto Thyroiditis should be based on a multidisciplinary approach wherein clinical, radiological, biochemical, cytological, and radionuclide parameters are taken into consideration. However, in spite of the availability of different diagnostic modalities, demonstration of lymphocytic infiltration on cytologic smears still remains the gold standard. The biochemical parameters are an adjunct to cytomorphological diagnosis and should be used to increase the diagnostic accuracy and reproducibility. Though there is strong correlation of antithyroid antibodies, especially Anti-TPO with Lymphocytic thyroiditis, the present study and previous similar studies have failed to establish any significant correlation between the cytological grades and these biochemical parameters. Cases with increased TPO and normal TSH should have a close follow-up so as to avoid any

deleterious effects of the disease. Fine Needle Aspiration Cytology (FNAC) findings and assay of serum Anti-Thyroid Peroxidase (anti-TPO) antibody have evolved as the major components in the investigations of thyroid nodules and diffuse thyroid enlargement.

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