

## Research Article

# Lymphocytic thyroiditis: a correlation of cytological grades with clinical, biochemical and ultrasound findings

P. Uma<sup>1</sup>, B.V.S. Kartheek<sup>1</sup>, S. Himaja<sup>1</sup>, J. Chandra Lekha<sup>1</sup>,  
A. Kasi Babu<sup>2</sup>, A. Bhagya Lakshmi<sup>1\*</sup>

<sup>1</sup>Department of Pathology, Andhra Medical College, Visakhapatnam, A.P., India

<sup>2</sup>Department of Biochemistry, Rajiv Gandhi Institute of Medical Sciences, Srikakulam, A.P., India

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### \*Correspondence:

Dr. A. Bhagya Lakshmi,

E-mail: dr.a.bhagyalaxmi@gmail.com

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## ABSTRACT

**Background:** Hashimoto's thyroiditis sometimes referred to as goitrous thyroiditis is a synonym of chronic lymphocytic thyroiditis or autoimmune thyroiditis. Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) is one of the most common cause of goiter and hypothyroidism, it is found most commonly in middle aged and young female, but can also occur in other age groups, including children. Chronic lymphocytic thyroiditis can be graded based on cytomorphology. In this study an attempt has been made to correlate the grades with clinical findings, biochemical levels and ultrasonography findings.

**Methods:** This is a prospective study conducted on 309 patients in the Department of Pathology, Andhra Medical College, Visakhapatnam. The various parameters like patient's clinical presentation, biochemical levels and thyroid ultrasound were studied. Fine needle aspiration of thyroid gland and grading of thyroiditis was done on smears. The grades were correlated with above parameters and the correlation indices were evaluated statistically. Chi-square tests were used for statistical correlation and p value of <0.05 was considered significant.

**Results:** Most of the patients were females (297, 96.11%) who commonly presented with a diffuse goiter (263, 85.11%). Asymptomatic cases (193, 62.46%) and elevated TSH (194, 62.78%) were common. Most of the cases had grade I/II disease (299, 96.76%) by cytology.

**Conclusion:** FNAC is a simple, safe and cost effective procedure and is a sensitive and specific diagnostic tool in diagnosing chronic lymphocytic thyroiditis. Cytological grading of chronic lymphocytic thyroiditis helps in assessing the severity of the disease and can predict the thyroid functional status. A combined approach of cytological grading of chronic lymphocytic thyroiditis along with ultrasonography and biochemical levels can detect subclinical hypothyroid states and provide a guide to therapy.

**Keywords:** Thyroiditis, Lymphocytic, Hypoechoic nodules

## INTRODUCTION

Lymphocytic thyroiditis (*struma lymphomatosa*) was first described by Haku Hashimoto in 1912, which bears his name. Chronic lymphocytic thyroiditis [Hashimoto's thyroiditis] is one of the most common causes of goiter and hypothyroidism. It is found most commonly in

middle aged and young females, but also occurs in other age groups, including children. Fine needle aspiration is a simple and cost effective procedure and plays a significant role in the diagnosis of chronic lymphocytic thyroiditis which is a non-surgical condition. Clinically chronic lymphocytic thyroiditis can present as a diffuse or nodular swelling being totally asymptomatic.

Thyroid dysfunction can be evaluated by measuring serum TSH, T<sub>4</sub> and T<sub>3</sub> levels, but significant changes in their levels are seen late in the disease process. Several studies have indicated 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 predictor of autoimmune process even when these disorders have not been suspected clinically.

Despite the availability of several tests for diagnosis of chronic lymphocytic thyroiditis, Fine Needle Aspiration Cytology (FNAC) remains the gold standard. In the present study an effort was made to grade chronic lymphocytic thyroiditis on FNAC smears and to know their significance in predicting thyroid injury by comparing with clinical, biochemical and ultrasonography findings.

## METHODS

This is a prospective study conducted in the Department of Pathology, Andhra Medical College, Visakhapatnam from October 2010 to September 2012. Out of 1573 thyroid aspirations done during the study period 414 cases of chronic lymphocytic thyroiditis were diagnosed on cytology of which 309 cases were included in the study based on inclusion and exclusion criteria.

**Inclusion criteria:** Newly diagnosed cases of chronic lymphocytic thyroiditis

### **Exclusion criteria:**

- 1) Subjects receiving either thyroxine or any other drug known to interfere with thyroid function at the time of evaluation.
- 2) Old cases of chronic lymphocytic thyroiditis.
- 3) Any other additional lesions observed in association with chronic lymphocytic thyroiditis diagnosed on cytology.

Thyroid function tests were used to determine blood concentrations of thyroid hormones. The patients had estimation of T<sub>3</sub>, T<sub>4</sub> & TSH (using immunoradiometric assay kit IRMAK-9 for TSH estimation and radioimmunoassay kits RIAK 4/4A & RIAK 5/5A for T<sub>3</sub> & T<sub>4</sub> estimation respectively). The reference range used was T<sub>4</sub>(55 – 135 ng/ml), T<sub>3</sub>(0.7 – 2ng/ml) and TSH(0.17 – 4.05 µIU/ml). Depending on these results patients were considered euthyroid, hyperthyroid, and hypothyroid.

Ultrasonography of thyroid gland was performed by a single sonologist who was blinded to the clinical and biochemical status of the subjects using high resolution ultrasound machine with 5 – 10 MHz Broad band linear transducer. A preselected set of sonographic features (hypoechoogenicity, micronodularity, echogenic septa, echogenic nodules <5mm and hyperechoic nodules >5mm) were taken for sonographic analysis.

Fine needle aspiration of the thyroid was done by using non aspiration technique. USG guidance was not used for the procedure. In case the material obtained was not satisfactory a repeat aspiration was done but not more than 2 aspirations were tried on each patient.

The cytology smears were seen by two independent pathologists. 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, epitheloid cell clusters, anisonucleosis or interlobular fibrosis that is the presence of fibrous tissue or scattered fibroblasts in the aspirate. 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 grading system<sup>2</sup>**

Grade morphological features

**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]:** Floride lymphocytic inflammation with germinal centre formation, very few follicular cells left.

**Statistical analysis:** Chi-square tests were used for statistical correlation and p value of <0.05 was considered significant.

## RESULTS

Duration of the study: 2 years i.e., from October 2010 to September 2012.

No. of cases analysed during the study period: 309 cases

Cases available for correlation between cytology and biochemical findings: 309 cases

Cases available for correlation between cytology and ultrasonography findings: 176 cases

Of the three hundred and nine patients data on all parameters were available in 176 cases (56.96%) only.

In the present study age of the patients ranged from 7 to 73 years [table 1]. 262 (84.79%) cases were in the age group of 10 to 40 years. In the present study, females far outnumbered males in the ratio of 24.75:1. The prevalence of juvenile lymphocytic thyroiditis (0-18 yrs) was 40 (12.94%) in the present study.

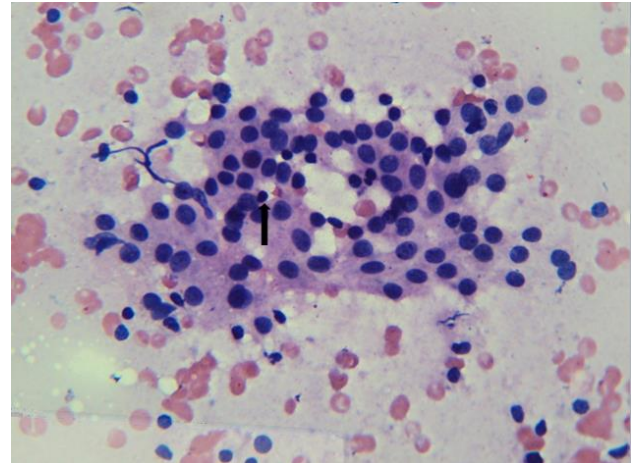
**Table 1: Age and sex distribution of 309 Subjects with chronic lymphocytic thyroiditis.**

Age Interval	Total Cases	Male	Female
0-10	2	0	2
11-20	62	6	56
21-30	123	1	122
31-40	88	4	84
41-50	18	0	18
51-60	12	0	12
61-70	3	1	2
71-80	1	0	1
Total	309	12	297

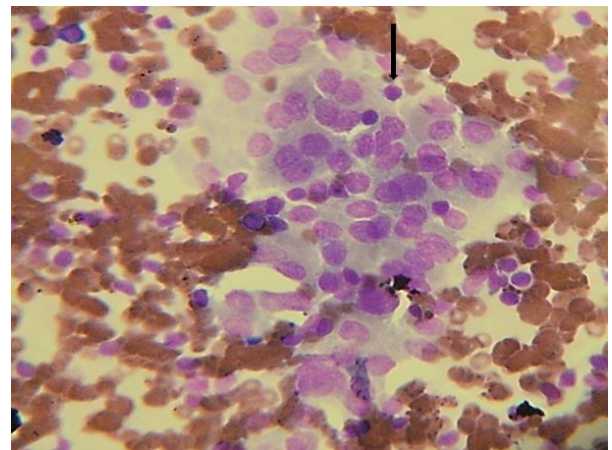
**Table 2: Cytological grading of chronic lymphocytic thyroiditis – 309 cases.**

Grades of Chronic Lymphocytic Thyroiditis	No. of Cases
I	128(41.42%)
II	171(55.34%)
III	10(3.24%)
Total	309

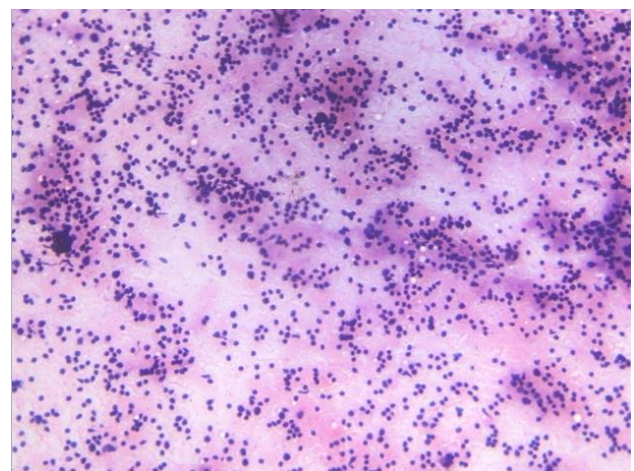
Grading of thyroiditis was done as per the criteria adopted by Bhatia et al<sup>2</sup> [table 2]. One twenty eight (41.42%) patients had mild lymphocytic infiltration of the gland and were graded as grade I thyroiditis (Figures 1, 2). One seventy one (55.34%) had grade II disease characterized by moderate degree of lymphocytic infiltrate with evidence of follicular destruction, Hurthle cell change, giant cells etc (Figures 3, 4). Grade III thyroiditis was noted in 10 (3.24%) patients characterised by dense lymphocytic infiltrates with germinal centres and with very few follicular cells left (Figures 5, 6). The polymorphic population of cells with lymphocytes, immunoblasts and plasma cells helped in distinguishing these cases from Non-Hodgkin's lymphoma.



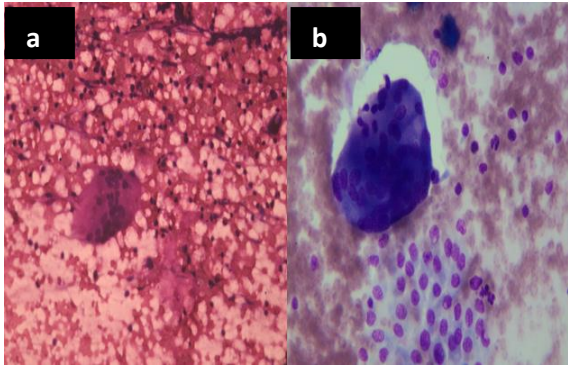
**Figure 1: Grade I lymphocytic thyroiditis showing thyroid follicular epithelial cells with mild lymphocytic infiltration (arrow). (H&E, 400X).**



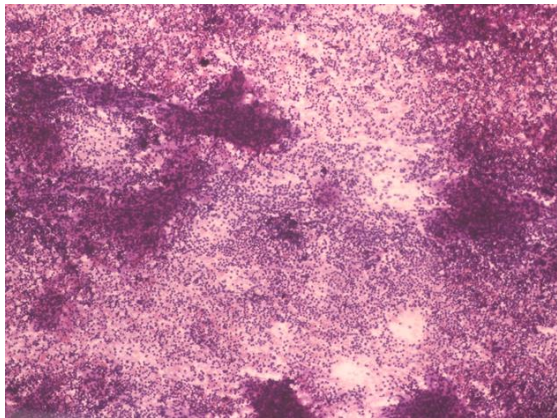
**Figure 2: Grade I lymphocytic thyroiditis showing thyroid follicular epithelial cells with mild lymphocytic infiltration (arrow). (MGG, 400X).**



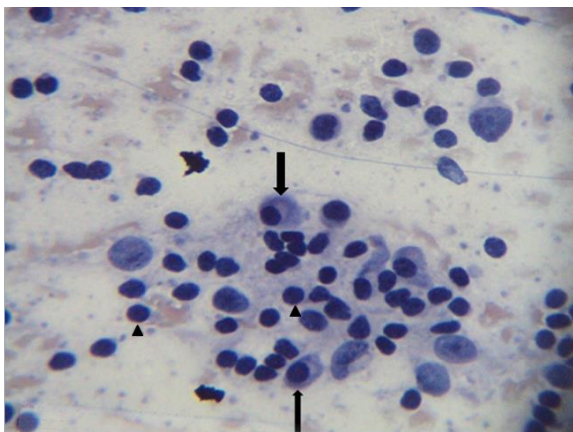
**Figure 3: Grade II lymphocytic thyroiditis showing thyroid follicular epithelial cells with moderate lymphocytic infiltration in the background. (H&E, 100X).**



**Figure 4: Grade II lymphocytic thyroiditis a) H&E (100X) – showing moderate lymphocytic infiltration and a giant cell. b) MGG (400X) –showing thyroid follicular epithelial cells, a giant cell and lymphocytes in the background.**

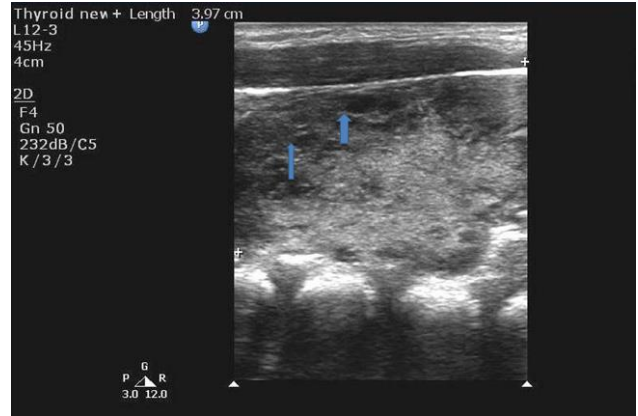


**Figure 5: Grade III lymphocytic thyroiditis with florid lymphocytic infiltration. (H&E, 40X).**



**Figure 6: Grade III lymphocytic thyroiditis showing lymphocytes (arrow heads) and plasma cell (arrows) infiltration. (H&E, 400X).**

In the present study out of the 309 cases 194 (62.78%) were biochemically hypothyroid, 93 (30.09%) euthyroid and 22 (7.12%) cases were hyperthyroid. Among the 40 cases of juvenile lymphocytic thyroiditis 27 (67.5%) showed biochemical evidence of hypothyroidism.



**Figure 7: Ultrasonography showing hypoechoic micronodules (arrows) in a case of lymphocytic thyroiditis.**



**Figure 8: A case of lymphocytic thyroiditis on ultrasonography showing diffuse hypoechoic changes.**

57 (61.29%) cases of biochemically euthyroid were observed in grade I lesions whereas, biochemically hyperthyroid cases were seen in grade I and grade II lesions with 13(59.09%) and 9(40.9%) cases respectively.

Out of 128 grade I lesions 57 (44.53%) cases were biochemically euthyroid, 58 (45.31%) cases were biochemically hypothyroid and 13 (10.16%) cases were biochemically hyperthyroid.

Out of 171 grade II lesions 34 (19.88%) cases were biochemically euthyroid, 128 (74.85%) cases were biochemically hypothyroid and 9 (5.26%) cases were biochemically hyperthyroid.

Out of 10 grade III lesions 2(20%) cases were biochemically euthyroid and 8(80%) cases were biochemically hypothyroid [table-3].

There was a statistical significance between the grades of lymphocytic thyroiditis and biochemical findings (p=0.001).

**Table 3: Comparison of grades of chronic lymphocytic thyroiditis with biochemical findings – 309.**

Grades of Chronic Lymphocytic Thyroiditis	Euthyroid	Hypothyroid	Hyperthyroid
I	57	58	13
II	34	128	9
III	2	8	0
Total	93	194(62.78%)	22

Ultrasonography was carried out in 176 cases and a preselected set of sonographic features were observed. The features observed were diffuse hypoechoic 50(28.41%), hypoechoicmicronodules 126(71.60%), echogenic nodules (<5mm)- 18(10.22%), echogenic septa 44(25%), hyperechoic nodules (>5mm)- 2(1.36%) and normal study 4(2.27%).[table 4]

Among the observed sonographic features hypoechoicmicronodules was the most commonly observed feature which constituted 126(71.60%) of all cases and diffuse hypoechogenicity 50(28.41%) was the second most commonly observed feature.

**Table 4: Comparison of grades with ultrasonography findings – 176 Cases.**

Grades of Chronic Lymphocytic Thyroiditis	Diffuse Hypoechoic	Hypoechoic Micronodules	Echogenic Nodules <5 Mm	Echogenic Septa	Normal Study	Hyperechoic Nodule >5 Mm
I	13	30	2	12	4	2
II	36	92	16	32	0	0
III	1	4	0	0	0	0
TOTAL	50(28.41%)	126(71.60%)	18(10.22%)	44(25%)	4(2.27%)	2(1.36%)

Hypoechoicmicronodularity observed were 30(63.83%), 92(74.19 %) and 4(80%) in grades I, II and III respectively, whereas diffuse hypoechogenicity observed were 13(27.66%), 36(29.03%) and 1(20%) in grades I, II and III respectively.

Echogenic septa 44(25%), echogenic nodules (<5mm)- 18(10.22%) were observed only in grade I and II lesions. In the present study on ultrasonography normal study 4(2.27%) and hyperechoic nodules (>5mm) - 2(1.36%) were observed only in grade I lesions.

In the present study correlation between grades and ultrasonography findings showed statistical significance (p=0.016).

## DISCUSSION

The aspiration smears of lymphocytic thyroiditis has wide spectrum of cytomorphological features, resembling a hyperplastic lymph node to a Hurthle cell neoplasm, basing on which cell is predominant. In the present study, an effort was made to relate these wide cytomorphological features of chronic lymphocytic thyroiditis with thyroid function and clinical manifestation.

In the present study 309 patients with cytological diagnosis of chronic lymphocytic thyroiditis were subjected for estimation of thyroid hormone levels and ultrasonography. The cytological smears were graded by

adopting grading system of Bhatia et al.<sup>2</sup> Various grades of lymphocytic thyroiditis on smears were compared with the biochemical levels and ultrasonographic features to known the extent of thyroid dysfunction. The results were tabulated with statistical significance.

In the present study the age of occurrence of lymphocytic thyroiditis ranged from 7-73 years. 88.34% of cases were in the age group of 11-40 years. Studies by Bhatia et al,<sup>2</sup> Singh et al,<sup>17</sup> Kumar et al,<sup>12</sup> Nguyen et al<sup>18</sup> and Friedman et al<sup>7</sup> showed age of the patients ranging from 6-60 years, 9-65 years, 7-45 years, 15-70 years, and 18-71 years respectively which was comparable with the present study. Most of the cases documented in the present study were somewhat younger (mostly in 3<sup>rd</sup> decade) than that described in the literature, and the youngest patient was 7 years old girl.

In the present study, the prevalence of juvenile lymphocytic thyroiditis (0-18 yrs) was 12.94%, majority of them (67.5%) showed biochemical evidence of hypothyroidism. In the study by Marwaha RK et al<sup>15</sup> the prevalence of juvenile lymphocytic thyroiditis was 26.8%.

In English literature it is widely held that lymphocytic thyroiditis is most prevalent in women in the 40 to 50 year age group.<sup>16,22</sup> In the present study, females far outnumbered males in the ratio of 24.75:1 which was significantly higher than that of studies by Bhatia et al<sup>2</sup>

and Singh et al<sup>17</sup> where F:M ratio were 11.6:1 and 14:1 respectively.

The patients were asymptomatic in 62.46% of cases and 31.71% of patients had symptoms of hypothyroidism, which is said to be the natural course of the disease.<sup>4,6</sup> Study by Singh et al<sup>17</sup> showed 63.3% asymptomatic cases and 36.7% hypothyroid cases. Study by Bhatia et al<sup>2</sup> showed 73.68% hypothyroid cases and 25% asymptomatic cases on clinical assessment.

Measurement of serum TSH levels is generally considered the best screening test for thyroid disease;<sup>11</sup> increased values usually indicate hypothyroidism, and decreased values usually indicate hyperthyroidism. This test has proved to be both sensitive and specific. It's very sensitivity, however, may create a dilemma, since some patients are found to have elevated serum TSH levels, suggesting hypothyroidism, but have normal levels of thyroid hormone, whether measured as free thyroxine (T4) or free T4 index.

An elevated TSH level with a normal free T4 level is referred to as subclinical hypothyroidism. The elevation of TSH levels reflects the sensitivity of the hypothalamic-pituitary axis to small decreases in circulating thyroid hormone; as the thyroid gland fails, the TSH level may rise above the upper limit of normal when the free T4 level has fallen only slightly and is still within the normal range. Subclinical hypothyroidism is seen in chronic lymphocytic thyroiditis, which is a matter of concern for therapy.<sup>23</sup>

On hormonal assay in the present study 62.78% of the patients were found to be hypothyroid, with 22% of them having subclinical hypothyroidism. Thirty percent (30%) of the patients were biochemically euthyroid and 7.12% were hyperthyroid. The prevalence of subclinical hypothyroidism was higher in our study compared to the studies by Singh et al<sup>17</sup> and Bagchi et al<sup>3</sup> where prevalence of subclinical hypothyroid cases were 19.3% and 8-17%.

Ultrasonography, which has proven valuable in clarifying number and size of thyroid nodules<sup>5,13</sup> can also be of value in the diagnosis of autoimmune thyroid disease (AITD) due to radiographic findings often associated with autoimmune thyroid disease (AITD).<sup>1,9</sup> Besides identification of thyroid nodules ultrasonography is able to characterize the echo structure of thyroid tissue in patients with autoimmune thyroid disease (AITD).<sup>8</sup> In autoimmune thyroid disease (AITD), lymphocytic infiltration and disruption of tissue architecture cause a reduction in thyroid echogenicity.

In the present study 176 cases were available for correlation between cytology and ultrasonography. Out of 176 cases 170 cases correlated with cytological diagnosis which showed a high positive predictive value of (96.6%) and sensitivity of 93.6%. The sensitivity of

ultrasonography in other studies has been reported to be 95.1%.<sup>14,19,20,24</sup>

In the present study micronodularity was the most frequently observed feature (71.6%) and showed a high positive value which is in keeping with the observations by previous studies by Yeh et al<sup>25</sup> and Bhatia et al.<sup>2</sup> 25% of the patients showed septations on ultrasonography indicating fibrosis and hence disease of some duration. Although non-specific, a diffuse hypoechoic pattern in a patient with lymphocytic thyroiditis has been shown to correlate with diffuse replacement of the gland by lymphocytes and fibrosis and is highly predictive of either the existence or the future development of hypothyroidism.<sup>14</sup> In the present study the prevalence of diffuse hypoechogenicity is seen in 28.4% which was comparable with previous studies (18-95%).<sup>14,19</sup>

The ultrasonography not only helps in diagnosis of the lymphocytic thyroiditis but also in selecting the patients with suspicious nodules for work up of malignancy.<sup>21</sup> In the present study no neoplastic lesion was found amongst the cases studied.

#### ***Cytological grading of lymphocytic thyroiditis***

The diagnosis of chronic lymphocytic thyroiditis was based on the evidence of inflammatory destruction of the follicular epithelial cells by the lymphoid cells, with or without the presence of Hurthle cell change. In the present study 309 cases of lymphocytic thyroiditis were graded semiquantitatively on cytology, analyzing and scoring such features as degree of lymphocytic infiltration, Hurthle cell change, giant cells and anisonucleosis as well as the background cell population.

The grading of chronic lymphocytic thyroiditis using the criteria adopted by Bhatia et al was found to be quite consistent and a high concordance rate was noted among the two observers. The grades were statistically correlated with clinical, biochemical and ultrasonography features.

Applying the simple, practical and easily applicable criteria devised by Bhatia et al in 2007, in the present study 309 cases of lymphocytic thyroiditis were categorized into Grade I, Grade II and Grade III thyroiditis in 4.42%, 55.34% and 3.24% of cases respectively.

#### ***Correlation of grades of lymphocytic thyroiditis with clinical features***

It was observed that many patients with grade I thyroiditis were asymptomatic (72.66%). High association of hypothyroid cases were observed in grade II and grade III thyroiditis. Hyperthyroid features were observed only in Grade I and II lesions.

Statistical correlation of grades of lymphocytic thyroiditis with clinical features was found to be significant ( $p = 0.002$ ).

### **Correlation of grades of lymphocytic thyroiditis with biochemical features**

It was observed that biochemical hypothyroid cases showed high association with grade II and grade III thyroiditis with majority of the grade III thyroiditis (80%) cases showed hypothyroidism. Majority of the biochemical euthyroid (61.29%) cases were seen in grade I lesions.

There was a statistical significance between the grades of lymphocytic thyroiditis and biochemical features ( $p=0.001$ ).

### **Correlation of grades of lymphocytic thyroiditis with ultrasound features**

Majority of the patients with grade III thyroiditis (80%) showed hypoechoic micronodules on ultrasonography. Echogenic septa were noted in grade I and grade II lesions with high association with grade II lesions. 4 (2.27%) cases showed normal study on ultrasonography which was observed in grade I thyroiditis. The normal echogenicity likely reflects a less severe degree of

lymphocytic infiltrate and fibrosis in the patient population than in patients with a hypoechoic gland.<sup>7</sup>

Correlation between the grades of lymphocytic thyroiditis and features on ultrasonography showed statistical significance ( $p=0.016$ )

Sensitivity of ultrasonography as screening test in predicting various grades of lymphocytic thyroiditis is 93.6 %.

Kumar et al,<sup>12</sup> attempted the semiquantitative grading of lymphocytic infiltration in auto-immune thyroiditis. These authors used a 2 tier grading system of 1) minimal and 2) moderate to heavy lymphocytic infiltration. In their series of 55 cases, 61.9% of the cases exhibited minimal and 38.1% had moderate to heavy lymphocytic infiltration. They found a statistically significant correlation between lymphocytic infiltration and the hormonal status of the patients ( $p=0.02$ ).

Study by Bhatia et al showed no significant statistical correlation between grades and clinical, biochemical and ultrasonography parameters. This may be due to their small sample size of 76 cases [table-5].

**Table 5: Comparison of the present study with other studies.**

Authors	No. of Pts.	Age	Sex	Hormonal Changes(%)-Hypothyroid	USG Findings	Cytological Grading
Kumar et al <sup>12</sup>	55	7-45 Yrs	55 F	72	-	Grade I-61.90% Grade II,III-38.1%
Jayaram et al	51	40-50 Yrs	40 F	45	30-Hypoechoic	Grade I-13.51% Grade II-62.16% Grade III-24.32%
Bhatia et al <sup>2</sup>	76	6-60 Yrs	70 F	98.68	48- Micronodules	Grade I-38.67% Grade II-44% Grade III-17.33%
Singh et al <sup>17</sup>	150	9-65 Yrs	140 F	58	-	Grade I-18% Grade II-26% Grade III-56%
Present Study	309	7-73 Yrs	297 F	62.78	50-Diffuse Hypoechoic 126-Hypoechoic Micronodules	Grade I-41.42% Grade II-55.34 % Grade III-3.24%

In the present study grading of lymphocytic thyroiditis on cytology correlated well with clinical, biochemical and ultrasonographic parameters which may be attributed to relatively large sample size.

### **CONCLUSION**

Chronic Lymphocytic Thyroiditis is the second most common thyroid lesion next to goiter and is one of the

most common cause of hypothyroidism. FNAC is a simple, safe and cost effective procedure and a sensitive and specific diagnostic tool in diagnosing chronic lymphocytic thyroiditis. Cytological grading of chronic lymphocytic thyroiditis helps in assessing the severity of the disease and can predict the thyroid functional status.

Asymptomatic and subclinical hypothyroid cases are associated with grade I and grade II chronic lymphocytic

thyroiditis on cytology, whereas overt hypothyroid cases are associated with grade II and grade III chronic lymphocytic thyroiditis. Elderly patients with grade III chronic lymphocytic thyroiditis [florid lymphocytic thyroiditis] on cytology can progress to lymphoma in long run and hence need follow up.

Reduction in thyroid echogenicity occurs at relatively early stage in autoimmune thyroiditis, often before overt thyroid failure and is a strong predictor of autoimmune process even when the disorder as not been suspected clinically. Among the observed sonographic features in the present study, hypoechoic micronodules was the most commonly observed feature and hypoechogenicity was the second most commonly observed feature associated with grade I and grade II lymphocytic thyroiditis on cytology. Ultrasonography can be used to screen the patient with chronic lymphocytic thyroiditis.

A combined approach of cytological grading of chronic lymphocytic thyroiditis along with ultrasonography and biochemical levels can detect subclinical hypothyroid state and provide a guide to therapy.

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