

# A Descriptive Study of Cytomorphological Grading of Hashimoto's Thyroiditis and Its Association with Thyroid Hormone Profile in a Tertiary Care Center in Mandya, Karnataka

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## ABSTRACT

### BACKGROUND

Thyroid diseases are the most common endocrine disorders throughout the world. Hashimoto's thyroiditis is an autoimmune thyroid disorder and it is the second most common thyroid lesion diagnosed on fine needle aspiration cytology (FNAC), only after goiter. FNAC is a quick, easy, safe, cost-effective and highly sensitive investigation for diagnosing Hashimoto's thyroiditis. The cytomorphological grading of Hashimoto's thyroiditis was 1<sup>st</sup> done by Bhatia et al. in 1912. The purpose of this study was to grade Hashimoto's thyroiditis cytomorphologically according to lymphocytic infiltration and correlating it with thyroid hormone profile.

### METHODS

This is a descriptive study of 87 cases which were diagnosed with Hashimoto's thyroiditis from January 2019 to December 2019 at the Cytopathology, Department of Pathology, MIMS, Mandya. The slides were collected, reviewed and graded according to Bhatia et al.'s grading system. Thyroid hormone values were collected from the department of biochemistry. The association between cytological grades and thyroid hormone parameters such as T3, T4, TSH and anti-thyroid peroxidase (anti-TPO) antibody were evaluated.

### RESULTS

In our study, female preponderance was noted. The age range in our study was 10 - 64 years and the majority of cases were in the age group of 21 - 40 years. Grade II was the most common cytological grade, followed by grade III. Based on thyroid function values, majority of the cases were hypothyroid, followed by euthyroid and remaining were hyperthyroid. Anti-TPO levels was raised in 80.6 %, most of them had hypothyroidism.

### CONCLUSIONS

In our study, there was no statistical association between cytological grades and thyroid hormone status.

### KEYWORDS

Hashimoto's Thyroiditis, FNAC, Bhatia et al.'s Grading, Anti-TPO Antibodies, FT3, FT4, Immunoassay Analyzer

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## BACKGROUND

Thyroid diseases are the most common endocrine disorders throughout the world.<sup>1</sup> Hashimoto's thyroiditis is an autoimmune thyroid disorder which is the second most common thyroid lesion diagnosed on fine needle aspiration cytology. Goitre being the most commonly diagnosed on FNAC. Hashimoto's thyroiditis was first described by Hakaru Hashimoto in 1912.<sup>2</sup> The other name for Hashimoto's thyroiditis is struma lymphomatosa.

It is the most common cause of hypothyroidism in developed countries whereas inadequate dietary intake of iodine is the most common cause of hypothyroidism worldwide.<sup>3</sup> The prevalence rate of Hashimoto's is 1 - 4 % and incidence is 30 – 60/100000 population per year.<sup>4</sup> The disease is more prevalent in female between age of 45 to 65 years. Female to male ratio of 10 : 1 to 20 : 1.<sup>5</sup> The occurrence of disease in young patients is due to iodine deficiency in non-coastal areas which is still prevalent despite national iodine deficiency diseases control program. In elderly, the disease may be seen in iodine sufficient areas. Many have linked increased incidence of Hashimoto's thyroiditis particularly in coastal areas due to excess intake of iodine.<sup>6</sup>

The symptoms of the Hashimoto's include painless enlargement of thyroid gland and features of hypothyroidism like fatigue, sensitivity to cold, constipation, pale and dry skin. After some years, the thyroid may shrink in size. The complications may include lymphomas. People with Hashimoto's thyroiditis can have family members with Hashimoto's. There is also a higher degree of association with other autoimmune disorders. On palpation, the thyroid can be firm, enlarged and can have lobulations or nodularity. On histopathology, there will be lymphocytic infiltration of the thyroid, varying from mild to dense infiltration with germinal centre formation. Atrophy of the thyroid follicles along with Hurthle cell change, absence of colloid and varying degrees of fibrosis.<sup>7</sup> The cytomorphological grading of Hashimoto's thyroiditis was 1<sup>st</sup> made by Bhatia et al.<sup>2</sup> The cytomorphological grading is based on lymphocytic infiltration.

FNAC is a quick, easy, safe cost-effective and highly sensitive investigation for diagnosing Hashimoto's thyroiditis. Fine needle aspiration cytology is a highly sensitive tool in diagnosing Hashimoto's (lymphocytic) thyroiditis, with a diagnostic accuracy rate of 92 %.<sup>6</sup> On cytology of Hashimoto's, there will be lymphocyte impingement into the thyroid follicles, with or without lymphocytes of varying degree, Hurthle cells, multinucleate giant cells and scant or absent colloid. Hurthle cells are large thyroid follicular cells with abundant, finely granular eosinophilic cytoplasm. Cytological diagnosis may be considered superior in initial stages of thyroiditis since the antibody production may be restricted to intrathyroidal lymphocytes and the spill over into blood has not taken yet.<sup>8</sup>

The most common laboratory findings in Hashimoto's thyroiditis are elevated levels of thyroid-stimulating hormone (TSH), low levels of free thyroxine (fT4) and increased antithyroid peroxidase antibodies. The antibodies attack the

thyroid tissue leading to inadequate production of thyroid hormones.<sup>3</sup>

Till date, association has not been noted in human studies between the severity of disease and the level of anti-TPO antibody concentration in serum. However, positive serum anti-TPO antibody concentration correlates with the active phase of the disease.<sup>3</sup>

The present study was designed to evaluate cytological grading of Hashimoto's thyroiditis using Bhatia et al.'s grading method and evaluating its association with thyroid hormone parameters and antibody profile.

### Objectives

- To grade Hashimoto's thyroiditis cytomorphologically according to lymphocytic infiltration. (Bhatia et al.'s grading system)
- To study the association of cytomorphological grading with thyroid hormone profile

## METHODS

The present study is a descriptive study made from the cases of Hashimoto's thyroiditis diagnosed from January 2019 to December 2019 (one year duration), conducted at the Cytopathology, Department of Pathology, Mandya Institute of Medical Sciences (MIMS), Mandya, Karnataka, India. All slides from patients who were diagnosed as Hashimoto's thyroiditis cytologically during this period was considered in the study. Simultaneously, the biochemical parameters (fT3, fT4, TSH) were also collected from the Department of Biochemistry, MIMS, Mandya. Any case with incomplete proforma was excluded from the study. So, a total of eighty-seven (87) cases were included in the study. These slides were taken from the patient who had underwent FNAC in our department and was diagnosed as Hashimoto's thyroiditis along with the availability of value of biochemical parameters (fT3, fT4, TSH, anti-TPO). Anti-TPO was not evaluated in all patients, it was done only in few patients.

Institutional ethical clearance was obtained before the start of study. Patient details regarding age, gender and slides (Giemsa stain and Haematoxylin and eosin stain) were taken from the register maintained at the department.

The procedure followed in our department for FNAC of thyroid was fine needle non-aspiration technique. It was with the help of a disposable 10 ml syringe fitted in a syringe holder and 22-gauge disposable needle. Needling was done without aspiration as thyroid is a rich vascular organ. After obtaining the material, smears were prepared. One smear was stained by Giemsa method and the other was stained with haematoxylin and eosin stain (H & E).

The cytological grading of FNAC smears was made according to lymphocytic infiltration, Hurthle cell change, giant cell and granuloma formation. Cytological grading and distribution of patients was studied.

Cytomorphological grading of Hashimoto's thyroiditis as per criteria given by Bhatia et al. (table 1)

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 clusters/giant cells/aniso nucleosis.
Grade III (severe)	Florid lymphocytic inflammation with germinal center formation, very few thyroid follicular cells left.

**Table 1. Bhatia et al.'s Grading for Hashimoto's Thyroiditis**

The values of biochemical parameters of free triiodothyronine, free tetraiodothyronine/thyroxine, thyroid stimulating hormone (TSH) and anti-thyroid peroxidase antibody were retrieved from the department of biochemistry of our institution. fT3, fT4 and TSH of all 87 cases were obtained and anti-TPO from 33 cases was obtained. The remaining cases did not have anti-TPO values.

T3, T4 and TSH were done by Abbott Architect i1000SR immunoassay analyser. Reference value of thyroid parameters followed in the biochemistry laboratory of our college were as follows,

- fT3 - 1.71 - 3.71 pg/ml,
- fT4 - 0.7 - 1.48 ng/ml,
- TSH - 0.35 - 4.94 µIU/ml,
- Anti - TPO < 5.61 IU/ml.

**Statistical Analysis**

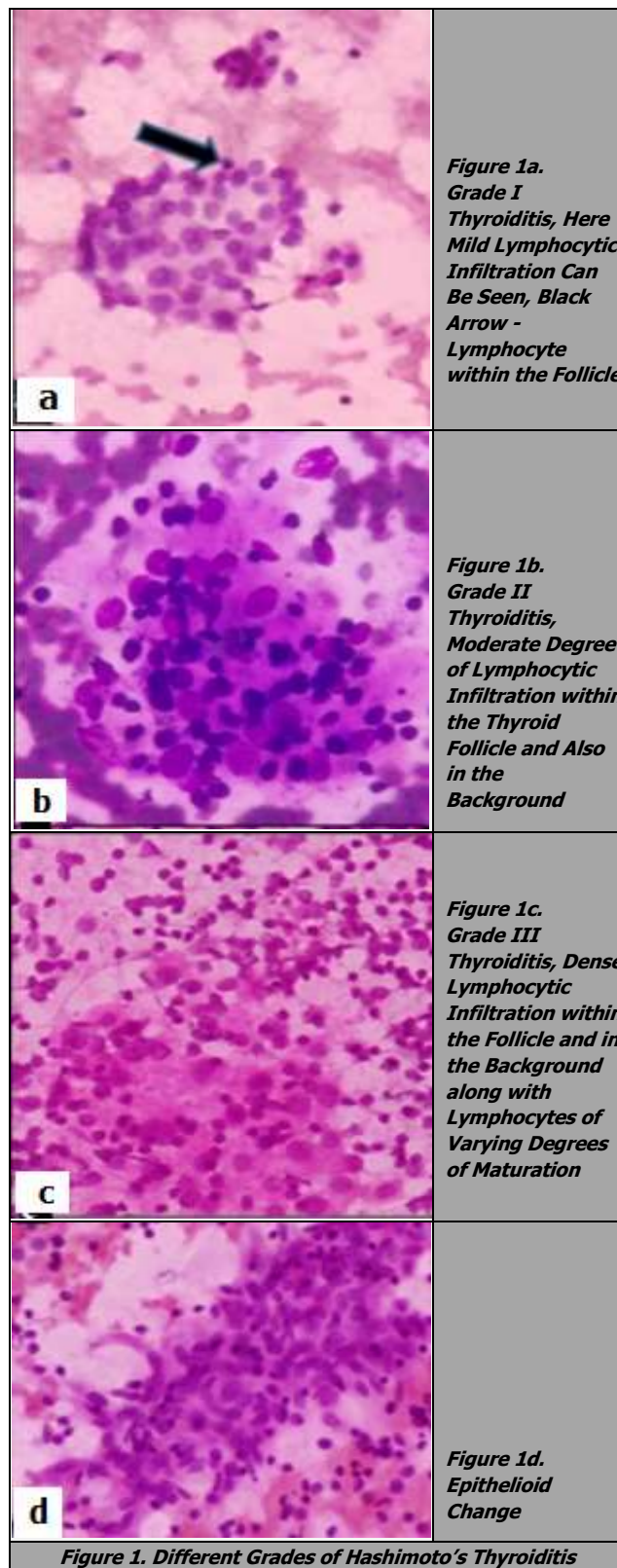
Data was analysed in Microsoft Excel 2010 and epi info version 7.0. Epidemiological details of the patient regarding age, gender, biochemical values of thyroid function including free T3, free T4, TSH, anti-TPO, cytological details, cytological grading and clinical thyroid status was entered on the Microsoft Excel sheet. The relation between cytological parameters and biochemical parameters were analysed with one another using appropriate statistical tests.

**RESULTS**

Total eighty-seven cases of Hashimoto's thyroiditis were included in the study. Females were 83 (95 %) cases and males were 4 (5 %) cases, female preponderance was noted (Table 2). i.e. the gender ratio is F : M = 21 : 1. The age group in the study ranges from 10 - 64 years, with majority of the cases were between 21 - 40 years constituting 46 cases (52.9 %). 24 cases (27.6 %) in the age group of 21 - 30 years and 22 cases (25.3 %) from the age group 31 - 40 years.

The next most common age group being 41 - 50 years constituting 16 cases (18.4 %). The age groups < 10 years and > / = 61 years were the least commonly affected in our study. (Chart 1). Juvenile lymphocytic thyroiditis is Hashimoto's thyroiditis/lymphocytic thyroiditis in the age group 0 - 18 years.

The prevalence of juvenile lymphocytic thyroiditis was 12.64 % (11 cases) in our study. The most common cytomorphological grade was grade II with 39 (45 %) cases, followed by grade III - 28 (32 %) cases and grade I with 20 (23 %) cases being the least common (Table 3). The microscopic image of different grades of Hashimoto's thyroiditis is shown in the figure 1.



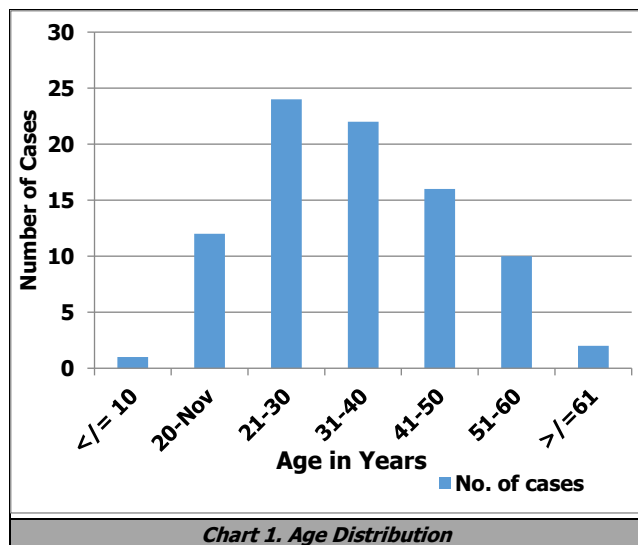
**Figure 1. Different Grades of Hashimoto's Thyroiditis**

Gender	Number of Cases (Percentage)
Male	4 (5 %)
Female	83 (95 %)

**Table 2. Gender Distribution**

Based on the thyroid function test values, the cases were classified into euthyroid, hypothyroid and hyperthyroid. Many of the cases were hypothyroid - 41 (47 %) cases, out of which 2<sup>nd</sup> most common is euthyroid - 30 (34 %) cases and least common was hyperthyroid - 16 (18 %) cases. The

association between thyroid hormone status and cytological grading was analysed and it was found that there is no association (table 4). The TSH level was raised in 13 (15 %) cases and was normal in 31 (36 %) cases. Anti-TPO levels were available in 33 cases and it was raised in 26 cases (78.8 %), most of which had hypothyroidism. The association between thyroid stimulating hormone, anti-TPO and cytological grades was analysed, and it was found that there is no association (table 5).



Grading	Number of Cases (Percentage)
I	20 (23 %)
II	39 (45 %)
III	28 (32 %)
<b>Total</b>	<b>87 cases</b>

**Table 3. Distribution of Cytomorphological Grades**

Grading	Euthyroid	Hypothyroid	Hyperthyroid	Total
I	5	10	5	20
II	15	17	7	39
III	10	14	4	28
<b>Total</b>	<b>30</b>	<b>41</b>	<b>16</b>	<b>87</b>

**Table 4. Relation of Cytological Grades with Thyroid Status**

$\chi^2$  value: 1.6363 d.f. = 4, P value is .08022 (not significant)

Anti - TPO and TSH	Grade I	Grade II	Grade III	Total
Anti-TPO and TSH increased	5	3	7	15
Anti-TPO increased, TSH normal	0	5	1	6
Anti-TPO increased, TSH decreased	2	2	1	5
Ant -TPO normal, TSH increased	0	2	1	3

**Table 5. Relation of Anti-TPO, TSH and Grades of Thyroiditis**

P value is .3892 (not significant)

## DISCUSSION

Chronic lymphocytic thyroiditis was described by Hakaru Hashimoto. Hashimoto's thyroiditis is also considered as a synonym of chronic lymphocytic thyroiditis or autoimmune thyroiditis including atrophic and non-goitrous thyroiditis.<sup>6</sup> Thyroid disorders are increasing nowadays worldwide. The thyroid disorders can be easily identified compared to other endocrine disorders because the enlarged gland is easily visible and the approach for diagnosis is also easy, so the treatment can also be initiated early. The frequency of the disease occurrence is more commonly seen among female

between age of 45 to 65 years. Females have a significantly chance of getting the disease when compared to males, the female to male ratio of disease is 10 : 1 to 20 : 1.<sup>5</sup> India is in transition state between iodine-deficient and iodine sufficient state. Approximately 91 % of the people have access to iodized salt. The prevalence of lymphocytic infiltration of thyroid increases thrice when iodine supplementation is given in iodine-deficient areas. Following supplementation, the prevalence of anti-TPO positivity raises to about 40 % in 5 years.<sup>7</sup>

The pathogenesis of lymphocytic thyroiditis is complex and it comprises of genetic, environmental and immunological factors. In India, if this transition is followed by spurt, autoimmune thyroid disorder is not known till date. In an Indian study which was done before iodination, the prevalence of thyroid autoantibodies in people aged more than 50 years was found to be 25.9 % and 7.7 % in females and males respectively. From a Delhi based study, anti-TPO antibody positivity was seen in 13.3 % of adult individuals (18 - 90 years) in the post iodination era. In a Kerala based study, the percentage was found out to be 16.7 % among adult individuals of urban coastal area. When individuals with abnormal thyroid values are not considered for the study, the prevalence of anti-TPO and anti-thyroglobulin antibodies were 9.5 % and 8.5 % respectively.<sup>8</sup> The occurrence of disease in young patients is due to iodine deficiency in non-coastal areas which is still prevalent despite national iodine deficiency diseases control program. In elderly, the disease may be seen in iodine sufficient areas. Many have linked increased incidence of HT particularly in coastal areas due to excess intake of iodine.<sup>6</sup>

Clinically it is characterized by initial phase of hyperthyroidism followed by chronic phase of hypothyroidism. During the initial phase, there will be antibody mediated destruction of thyroid follicles and lymphocytic infiltration. During the chronic phase, there will be few atrophic thyroid follicles along with fibrosis of thyroid parenchyma. So, based on the stage of the disease, the patient can present with either features of hypo or hyperthyroidism.<sup>9</sup>

In our study, we have evaluated the association between cytomorphological grades and biochemical profile (TSH, anti - TPO). The age range in our study was 10 - 64 years with predominant cases being females. The female preponderance was similar to many studies in the literature. It was found that the reason for female preponderance is female sex steroid hormones and X chromosome containing a number of sex and immune related genes.<sup>7,10,11</sup>

The most common age group was 21 - 40 years which was comparable with study made by Sharma et al.<sup>7</sup> The prevalence of juvenile lymphocytic thyroiditis (0 - 18) was 12.64 % (11 cases). It was comparable with studies made by other authors.<sup>8,12,13</sup> In India, the prevalence of juvenile lymphocytic thyroiditis is higher in comparison to foreign countries, the possible explanation for this is high prevalence of iodine deficiency in Indian children.<sup>8,9,14</sup>

On grading according to the Bhatia et al. grading system, many cases belong to grade II which is similar to studies by other Indian authors. Hurthle cell change was seen in 74 % of cases which is similar to other studies.<sup>8,15,16,17</sup> Friedman M

et al. had described in his study that 98 % of cases have Hurthle cells characteristically in Hashimoto's.<sup>8,16</sup>

Most of the cases in our study were hypothyroid (47 %) similar to other studies. 18 % of the cases were hyperthyroid. In our study, it was observed that, as the cytological grade of Hashimoto's thyroiditis increases, the patient tends to have hypothyroid status. This probably suggests that the chronicity of disease leads to more and more destruction of thyroid follicles leading to hypothyroid status.

Anti-TPO levels were increased in 78.8 % cases among those who had their anti-TPO levels done. Anti-TPO negative cases can be explained on the basis of localized antibody production by intrathyroidal lymphocytes.<sup>10,17</sup> Out of 26 patients with raised anti-TPO antibody, 15 were hypothyroid, 6 were euthyroid and 5 were hyperthyroid. Similar observation was seen in other studies.<sup>10</sup> In our study, among the raised anti-TPO cases, most of them were of grade III (46 %), followed by grade I (33.3 %) and then grade II (20 %).

This was similar to study by Sood N et al.<sup>4</sup> In our study, higher the grade of lymphocytic infiltration, higher the anti-TPO positivity.

This tells us that our patient presents with raised anti-TPO in later stages. This was in contrast to studies by other authors where raised anti-TPO was more commonly associated with grade I.<sup>8</sup>

Among 16 hyperthyroid cases, 5 had increased anti-TPO. In that, 2 cases were grade I, 2 cases were grade II and 1 case belonged to grade III. This can be explained as, in early stage of the disease, there will be release of hormone into the circulation due to antibody mediated follicular destruction resulting in hyperthyroidism.<sup>8,9,18</sup>

## CONCLUSIONS

The most common age group affected by Hashimoto's thyroiditis in our study was 21 - 40 years with female preponderance. The most common cytological grade was grade II. Cytological grading of Hashimoto's thyroiditis explains the pathogenesis of disease. As the grading advances, hypothyroid status and raised anti-TPO levels are seen more commonly. Most of the cases were hypothyroid. Anti-TPO antibody levels was increased in most of the patients who had got their antibody levels done. There was no significant statistical association between cytological grades and thyroid hormonal status.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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