

# Hashimoto's Thyroiditis – A Malaysian Perspective

Jayaram G\*, Iyengar KR\*, Sthaneshwar P#, Hayati JN\*\*

## Abstract

*This study was undertaken to analyze the fine needle aspiration (FNA) cytologic, functional and immunologic features in Hashimoto's thyroiditis (HT) with special reference to ethnicity in Malaysian patients. 88 cases of HT retrieved from the archives of the cytology laboratory were reviewed. Ethnic, clinical, cytologic, biochemical, and immunologic features were correlated. HT was more common in Indian patients (57%). 33% of HT cases presented with nodular thyroid enlargement (47.5% were Chinese). 57.5% were euthyroid and 35% hypothyroid. Thyroglobulin antibody (TG Ab) and thyroid peroxidase antibody (TPO Ab) (tested in 29/88 cases) were elevated in 83% and 93% cases respectively. Review of cytologic smears showed Hurthle cells in 56% cases, high lymphoid to epithelial ratio in 38%, lymphoid follicles in 67%, follicular cell infiltration by lymphoid cells in 69% and lymphohistiocytic clusters in 40%. Giant cells and/or granulomas were present in 45% and plasma cells and/or immunoblasts in 40% of cases. 17% showed neutrophils and/or eosinophils infiltrating follicular epithelial cells. Follow up FNA of eight cases showed appearance of a diagnostic cytologic pattern in all and changes in clinical presentation in four. Hashimoto's thyroiditis was more common among Indian women with nodular presentation seen more often in Chinese. Hurthle cell change, lymphoid follicles and follicular cell infiltration by lymphoid cells, considered histologic hallmarks of HT, were seen less frequently. 17% cases showed infiltration of follicular cells by neutrophils and eosinophils, a hitherto undescribed feature in HT. Follow up cytology was helpful in monitoring progression of disease and arriving at a definitive diagnosis.*

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**Key Words :** Fine needle aspiration cytology, Hashimoto's thyroiditis.

## Introduction

The value of FNA cytology and its role in the management of solitary thyroid nodules is undisputed.<sup>1-3</sup> Often overlooked however, is the role of FNA in preventing unnecessary surgery, especially in thyroiditis.<sup>4-7</sup> An earlier review of FNA cytology service in our department had shown nodular goiter to be the most common cause of thyroid enlargement with neoplasms accounting for about 12% and thyroiditis about 5%.<sup>8</sup>

Hashimoto's thyroiditis (HT) is more prevalent in Asians.<sup>9-11</sup> Malaysia and Singapore boast a multiethnic population comprised variously by people of Malay, Chinese, and Indian origin. Casual observation at the

FNA clinic had indicated a greater frequency of thyroiditis among patients of Indian origin. A 1993 Singapore study in pregnant women showed goiter to be more frequent among Indians.<sup>9</sup>

The present study correlates FNA cytologic features of HT with thyroid function and antibody profile among Malaysian patients with special reference to ethnic differences.

## Materials and Methods

Records of 88 cases of HT diagnosed on FNA cytology at the Faculty of Medicine, University of Malaya, Kuala Lumpur, between January 1995 and December 2005 were retrieved. Race, age, sex and clinical presentation (diffuse or nodular enlargement

\*Professor and Consultant Pathologist, \*Associate Professor, #Senior Lecturer, \*\*Cytotechnologist, Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

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**Corresponding Author:** Krishnan R Iyengar, Department of Pathology, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.

**E-mail:** drkrishnan@um.edu.my

of thyroid) were tabulated along with Free T4 and TSH values and titres of thyroglobulin antibody (TG Ab) as well as thyroid peroxidase antibody (TPO Ab). Free T4 and TSH were measured by chemiluminescence method using ADVIA Centaur® immunoassay system (Bayer Healthcare LLC, NY, USA) while the autoantibodies were measured by ELISA using QUANTA Lite™ Thyroid T and Thyroid M (INOVA Diagnostics Inc, CA, USA). The normal range for T4 was taken as 11.5 to 23.2 pmol /L and for TSH as 0.40 to 5.50 pmol /L. Calculated optical density of more than 0.6 units for anti-thyroid antibodies was considered abnormal. The FNA cytologic smears stained by May-Grünwald Giemsa were reviewed and the following cytologic features were recorded: presence of colloid in the background, degree of cellularity, pattern of arrangement of follicular cells (clusters/acinar/dissociated/3 dimensional), presence of nuclear atypia, lymphoid follicles, lymphohistiocytic clusters, lymphocytes infiltrating follicular cells, Hurthle cells with and without nucleoli and atypia, giant cells, granulomas, fire flares and/or paravacuolar granules. Lymphocytes, eosinophils, neutrophils, plasma cells and immunoblasts were scored semiquantitatively as nil, 1+, 2+, 3+ and 4+. The ratio of lymphoid to epithelial cells (L:E Ratio) was also noted. Available follow up data was also reviewed.

### Observations

Indians formed the majority of patients (57%) followed by Chinese (24%) and Malay (19%). 29 cases (33%) of HT presented with nodular thyroid enlargement. 76% of Indians had diffuse thyromegaly (Table 1) whereas nodular presentation was most prevalent in Chinese (47.5%). T4 and TSH values were available in 68 patients. 33 cases (48.5%) were biochemically euthyroid while 27 (39.7%) were hypothyroid (8 of these were subclinical). Eight cases

(11.7%) were hyperthyroid (4 of these were subclinical). One patient of HT presenting with normal values later developed low TSH while another patient with high T4 and TSH was on L-thyroxin therapy for hypothyroidism. Thyroid autoantibody testing was done in 29 cases of HT. TG Ab was elevated in 24 (83%) and TPO Ab in 27 (93%). No ethnic difference was apparent with respect to thyroid function or antithyroid antibodies.

Smear background showed blood often admixed with colloid or lymphocytes. Follicular cellularity was good or moderate in 49/88 cases (56.6%) with cells mostly arranged in clusters or acinar pattern. One case showed three-dimensional clusters while in another cellularity was scanty. L: E ratio was recorded in 61 cases where follicular epithelium as well as background lymphocytes were represented in the smears. L: E ratio was high (Fig. 1) in 23 cases (38%) and low in 24 (39%). 14 cases (23%) showed fairly equal proportions of epithelial and lymphoid cells. Lymphoid follicles (Fig. 2) were present in 59/88 cases (67%), lymphocytes infiltrating follicular epithelial cells

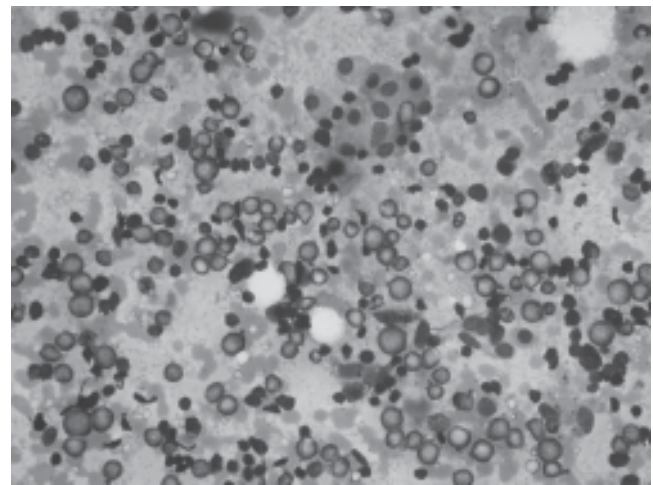


Fig. 1: High lymphoid:epithelial ratio (MGG, x 400).

**Table 1 : Comparison of clinical and laboratory features of HT among different ethnic groups**

Clinicopathological features of HT	Chinese [n=21(%)]	Indian [n=50(%)]	Malay [n=17(%)]
Nodular presentation	10 (47.5)	12 (24)	7 (41)
Hurthle cells	15 (71.5)	26 (52)	8 (47)
Lymphoid follicles	16 (76)	31 (62)	12 (70.5)
Follicular/Hurthle cell infiltration by lymphoid cells	15 (71.5)	38 (76)	8 (47)
Thyroid function	[n=17(%)]	[n=39(%)]	[n=12(%)]
Hypothyroid	8 (47)	15 (38.5)	4 (33)
Euthyroid	8 (47)	18 (46.1)	7 (59)
Hyperthyroid	1 (6)	6 (15.4)	1 (8)
TG Ab elevated	n=6(%)	n=18(%)	n=5(%)
	6 (100)	13 (72)	5 (100)
TPO Ab elevated	5 (83)	17 (94)	5 (100)

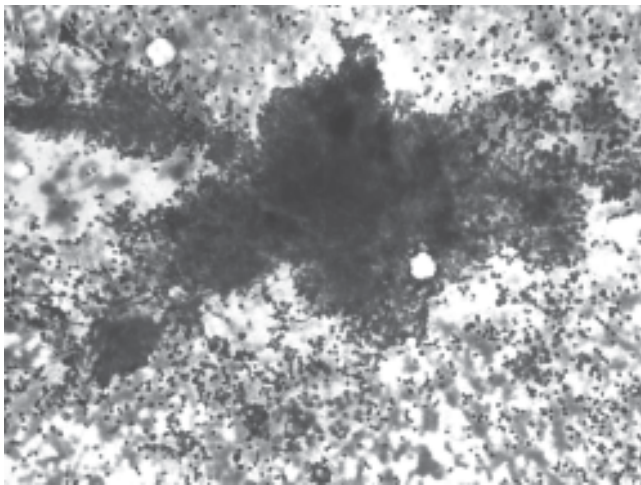


Fig. 2: Lymphoid follicles in HT (MGG, x 400).

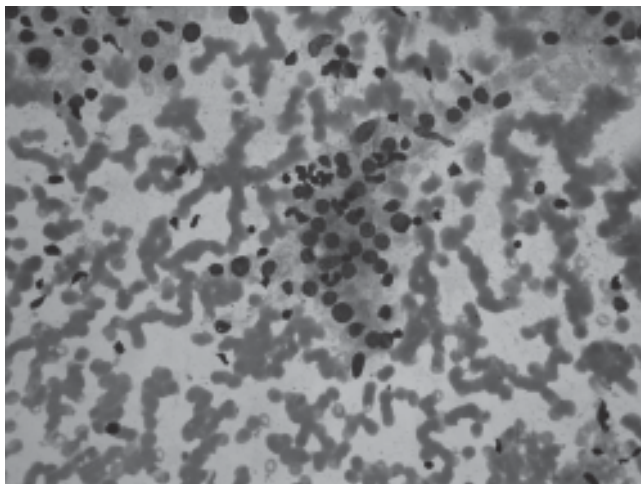


Fig. 3: Follicular cell infiltration by lymphoid cells (MGG, x 400).

(Fig. 3) in 61 (69%) and lymphohistiocytic clusters in 35 (40%). All three of these features were present in only 21 (24%) cases while they were all absent in 10 (11%). Presence of lymphoid follicles and lymphocytes infiltrating follicles were seen with nearly equal frequency in the various ethnic groups.

Of 49 cases (56%) showing Hurthle cell populations (Fig. 4), 34 (69%) showed lymphoid follicles; 38 (77.5%) showed lymphocytes infiltrating follicular cells and 19 (39%) had lymphohistiocytic clusters. Hurthle cells were observed more frequently among the Chinese (71.5%).

Multinucleated giant cells and/or granulomas were seen in 40 cases (45%). Plasma cells and/or immunoblasts were present in 35 cases (40%). Neutrophils and/or eosinophils were seen infiltrating follicular epithelial cells (Fig. 5) in 15 cases (17%). Fire flares and/or paravacuolar granules were present in 21 cases (24%).

Table 2 shows salient clinical, biochemical,

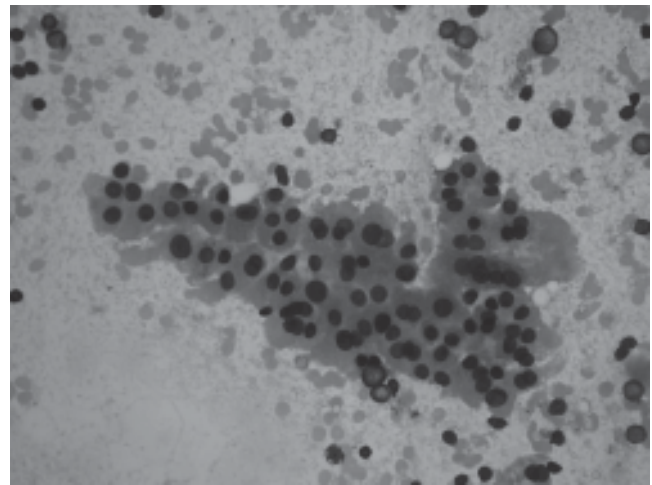


Fig. 4: Hurthle cells in HT (MGG, x 400).

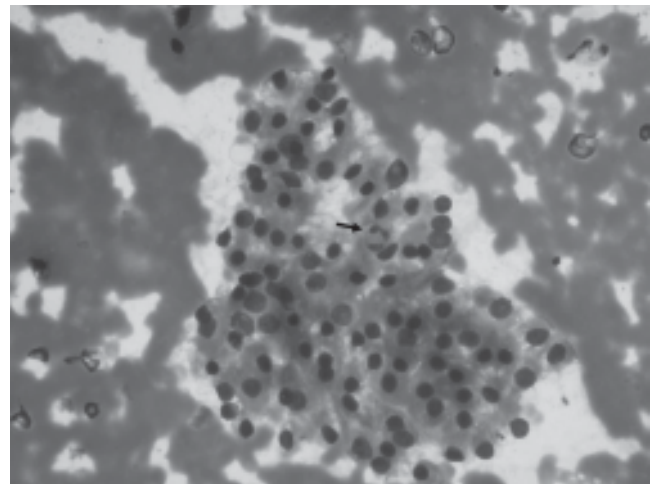


Fig. 5: Follicular cell infiltration by eosinophils (MGG, x 400).

immunologic and cytologic features of eight cases with follow up FNA. Reasons for follow up FNA (in most cases recommended by the cytopathologist) were non-diagnostic cytologic picture or high cellularity of follicular or Hurthle cells leading to difficulty in ruling out a neoplastic process.

Case No. 1 was lost to follow up after initial FNA in 1999 until 2005 when she had two FNAs. Follow up in other cases ranged from 6 months to 2 years. These cases demonstrated change in clinical presentation from diffuse to nodular in 3 cases and vice versa in one. Lymphoid follicles (3 cases), lymphohistiocytic clusters and giant cells (4 cases each) made an appearance.

## Discussion

The present study confirms the higher prevalence of HT among Indian patients in our hospital (57%) with ethnic Malay:Chinese:Indian distribution of 1:1.2:2.9 whereas the patient attendance ratio at our hospital is 1:1.5:0.8 for the same groups. Given the

**Table 2 : Summary of clinical and laboratory features in follow up cases of HT**

Cytologic parameter	Case 1			Case 2		Case 3		Case 4		Case 5		Case 6			Case 7		Case 8	
	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>
Follow up	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>
Clinical appearance	Nd	D	D	Nd	Nd	D	Nd	D	Nd	Nd	Nd	D	D	Nd	D	D	D	D
Lymphoid follicles	-	+	+	+	+	-	+	-	+	+	+	-	-	-	+	+	-	-
Lympho-histiocytic Clusters	-	-	-	-	+	-	+	-	+	+	-	-	-	+	-	-	-	-
Lymphocytes infiltrating follicular cells	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hurthle cells	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Giant cells	-	-	-	-	+	-	+	-	+	-	+	-	-	-	+	+	+	+
Granulomas	-	-	-	-	-	-	-	-	-	Few	Many	-	-	-	+	+	-	-
L:E ratio	2:1	-	1:5	1:4	1:2	-	2:1	1:5	1:5	1:3	1:4	-	-	-	2:5	2:5	1:3	-
Diagnosis	HT	FLH/HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HCL	Early HT	HT	HT	Early HT	HT	HT
T4 Range	N	N	NT	L	L	N	NT	L	L	N	NT	N	L	L	N	NT	N	N
TSH Range	N	N	NT	H	N	L	NT	H	H	N	NT	N	N	N	N	NT	N	L
TG Ab	H	H	NT	H	H	H	NT	H	NT	NT	NT	NT	H	H	H	NT	NT	NT
TPO Ab	H	H	NT	H	H	H	NT	H	NT	NT	NT	NT	H	H	H	NT	NT	NT

Nd: nodular; D: diffuse; FLH: follicular hyperplasia; HCL: Hurthle cell lesion; L:E ratio: lymphoid:epithelial ratio; TG Ab: thyroglobulin antibody; TPO Ab: Thyroid peroxidase antibody; NT: not tested; N: normal; H: high; L: low.

fact that ethnic Indians constitute only 7.7% of the population in Malaysia, this observation assumes greater significance.<sup>12</sup> Goiter during pregnancy accompanied by high serum TSH was found to be more prevalent in Indian women (61%) in a study on antenatal patients in Singapore.<sup>9</sup> No significant racial difference was seen among pregnant women with regard to thyroid autoantibodies in that study.

As reported previously in HT, nodular presentation was seen in about a third of cases (33%). Transformation from diffuse to nodular goiter in 3/8 cases with follow up, could possibly be due to the cycle of regeneration and retrogression. TG Ab and TPO Ab were within the reference range in 17.3% and 7% cases respectively. Absence of serum antibodies in some cases of HT has been explained on the basis of demonstration of localized autoantibody production by intrathyroidal lymphocytes.<sup>13-15</sup> Our observation of larger number of cases showing TPO Ab than TG Ab (93% vs 82.7%) concurs with the concept of higher specificity of the former in HT.<sup>15</sup>

L:E ratio is characteristically high in HT<sup>16-21</sup> ranging from 2:1 to 10:1 with smear cytology in florid cases mimicking reactive lymphoid hyperplasia.<sup>21</sup> In the present study, 60% of cases showed large numbers of lymphoid cells in the smear background with high L:E ratio in 40%.

Hurthle cells were present in 56% of cases, significantly less than in previous reports.<sup>16-21</sup> In 15

cases where Hurthle cells were absent, antibody results were available. 10 of these showed elevated TG Ab and 14 elevated TPO Ab. One patient had normal antibody levels. Other features considered histologically characteristic of HT<sup>22</sup> were absent in cytologic material (lymphoid follicles: 33%; lymphoid cell infiltration of epithelial cells: 30.5% and lymphohistiocytic clusters: 60%). Multinucleated giant cells and/or epithelioid cell granulomas were present in nearly 40% of HT cases. Cytomorphologic features of the present series are compared with previous studies in Table 3.

Plasma cells were present in 21 (23%) and immunoblasts in 25/88 cases of HT(28.4%). Given that T cells are the predominant population of intrathyroidal lymphocytes in HT with B cells confined to germinal centers,<sup>23-25</sup> the relative infrequency of plasma cells seems reasonable.<sup>16-21</sup> B cell/plasma cell predominant lymphoepithelial-like lesions in advanced HT may be a manifestation of low grade MALToma.<sup>25-27</sup> It is tempting to speculate at this point whether B cell/plasma cell predominant lesions may be a marker for subsequent progression to lymphoma.

Infiltration of epithelial cells by neutrophils and/or eosinophils (seen in 17% of our cases) has not been reported previously. Whether this indicates a pathogenetic mechanism is to be considered. Fireflares (seen in less than a quarter of our cases), have been reported before and does not reflect Hashitoxicosis unless extensive.<sup>16</sup>

**Table 3 : Comparison of cytologic features of HT in various studies**

Cytologic feature	Jayaram et al <sup>16</sup> (1987)	Friedman et al <sup>17</sup> (1981)	Kini et al <sup>18</sup> (1981)	Bhalotra et al <sup>19</sup> (1990)	Present series (2006)
Number of cases	40	40	87	68	88
Nodular presentation	Few	80%	22%	Not recorded	33%
Hurthle cells	Many	98%	Variable	Rare	56%
Follicular cell atypia	Mild-moderate	Present	Often	Some cases	44%
Lymphoid follicles	Not recorded	Present	Present	Not recorded	Present (67%)
Follicular cells infiltrated by lymphocytes	Present	Not recorded	Present	Present	69%
Plasma cells	Not recorded	Present	Present	Present	Present (23%)
L:E ratio	High	High	High	High	high
Giant cells	33%	Infrequent	Rare	25%	39%
Granuloma	8%	Not recorded	Not recorded	50%	16%
Fireflares	25%	Not recorded	Not recorded	Most cases	23%

This study brought out interesting ethnic differences in Hashimoto's thyroiditis such as high prevalence among Indians and increased frequency of nodular presentation and Hurthle cell populations in Chinese. To the best of our knowledge, these variations have not been documented.

In the present study, in cases with cytomorphologic overlap with subacute thyroiditis (SAT) or Grave's disease (GD), where functional and immunological profile of the patient was not available, the clinician was advised to send the patient for follow up FNA after detailed clinical review and further investigations. The concordance rate was however, variable depending on clinician and patient factors. Overlap between the cytomorphologic features of HT, GD and SAT have been observed earlier<sup>19</sup> and biochemical alterations may at times be confounding. In four patients with biochemical hyperthyroidism (raised or normal T4 and low TSH), two showed cytomorphologic features common to HT and GD (high cellularity, lymphoid cells in the background and/or lymphoid follicles). However, a high L:E ratio, follicular infiltration by lymphoid cells and absence of fire flares ruled out GD; absence of giant cells and granulomas and high antibody levels ruled out SAT.

Giant cells and/or follicular infiltration by neutrophils in two other cases suggested the possibility of SAT. However, giant cells were few, granulomas absent and lymphoid follicles and lymphoid infiltration of follicular cells were present, helping to rule out SAT. GD was ruled out by a high L:E ratio, follicular degeneration and absent fire flares.

Of 20 cases where thyroid function and autoantibody were not tested, 5 showed fire flares, but GD was ruled out on the basis of high L:E ratio

and/or follicular infiltration by lymphoid cells. In 1/5 of these cases, as also in 15 cases where no fire flares were seen, occasional giant cells and granulomas were present. Here SAT was ruled out by the presence of lymphoid follicles and lymphoid infiltration of follicular cells.

Follow up of eight cases in this study showed the pattern of clinical presentation changing from diffuse thyromegaly to nodular in three. Likewise change from non-diagnostic cytomorphology to better defined characteristics such as the appearance of lymphoid follicles, follicular cell infiltration by lymphoid cells and increasing numbers of giant cells enabled a definitive diagnosis of HT in cases previously diagnosed as "Hurthle cell lesion" or "suggestive of HT". Cytodiagnosis in these cases was supported by demonstration of raised antithyroid antibodies. This underscores the role of FNA cytology in morphologically evaluating evolutionary stages of the autoimmune process and its utility in the follow up of cases with equivocal clinico-cytologic presentation.

This Malaysian hospital based study of HT showed interesting clinical and cytologic differences in various ethnic groups besides revealing variant cytomorphologic patterns, which to the best of our knowledge, have been addressed for the first time.

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