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Original Article

Pathology Section

Clinicopathological Study of Hashimoto Thyroiditis

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ABSTRACT

Introduction: Thyroiditis comprises various group of disorders with some form of thyroid inflammation. Hashimoto thyroiditis is the most common and clinically significant type of thyroiditis seen commonly in middle age females and also one of the most common cause of goitre seen in iodine sufficient regions. Endemic goitre a major health problem, still prevalent in various regions of india even after implementation of widespread national salt iodisation programme by Government of India. This study performed in tertiary centre of western coastal area where seafood is the staple diet of large number of people and inspite of widespread use of iodised salt large number of patients dignosed with HT. The proposed study is intended to further establish the role of histopathological study along with its correlation with clinical, biological and radiological parameters in the diagnosis of Hashimoto thyroiditis.

Aim: To record the morphological features along with its correlation with clinical, biochemical and ultrasonographic picture of this disease in western coastal endemic area for goitre and document morphological variation, if any and also to identify any thyroid neoplasm that may develop in the background of HT.

Materials and Methods: In this retrospective study records of patients with histological diagnosis of Hashimoto thyroiditis was conducted with respect to their clinical presentation, thyroid profile, antibody titre and ultrasonographic features.

Results: A total 55 patients with histopathological diagnosis of HT were included in the study. The histological slides were reviewed and reclassified into two groups based on hurthle cell change. Thus, 35 cases were diagnosed as HT while remaining were categorised as chronic lymphocytic thyroiditis. Ninety seven percent of patients were females and majority of them presented within 5 years of onset of symptoms. An amount of 68% patients had diffuse goitre, 33% were clinically euthyroid and 60.6% were biochemically hypothyroid. Antibody titre were elevated in 78% patients. In most of the cases USG picture showed hypoechogenecity with increased vascularity. Histopathological features were diagnostic and characteristic.

Conclusion: In the present study majority of patients were females in the middle age group with clinical presentation of diffuse goitre and inspite, of widespread use of iodised salt in this studied population large number of patients diagnosed with Hashimoto thyroiditis. Therefore, author conclude that all females of middle age group in an endemic area for goitre should be screened and also histologically confirmed by biopsy for this thyroiditis.

Keywords: Goitre, Iodine, Thyroid gland

INTRODUCTION

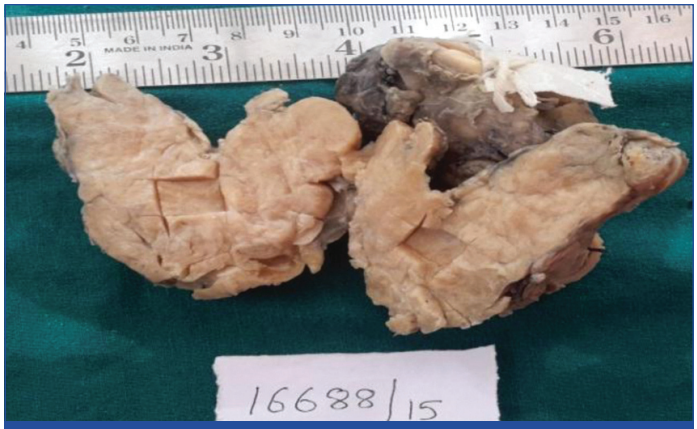
Thyroiditis consist of various disorders characterised by thyroid inflammation. Hashimoto Thyroiditis (HT) is the most common and clinically significant types of thyroiditis, seen commonly in middle age females. It is the most common cause of goitre in iodine sufficient areas [1]. After all the Goverment run national salt iodization programme, endemic goitre is still prevalent in India. [2] The reason for which is not fully understood though. To name a few, genetic predisposition of Indian population for autoimmune goitre and animal studies [3,4].

It has been noticed that iodine supplementation in iodine deficient areas increases the lymphocytic infiltration of thyroid gland by three fold along with increase in serum level of antithyroid antibodies [5]. This study done in western coastal area where the seafood is the staple diet of the population and there is a widespread use of iodised salt in the population. In spite, of this area known for endemicity of goitre and large number of patients diagnosed with HT. Clinically, it presents as diffuse or nodular swelling being asymptomatic or with symptoms of hypothyroidism. The biochemical evaluation of autoantibody titres, together with clinical, radiological and hormonal assay guides the clinician towards making a diagnosis of HT which can be confirmed on histopathological examination. Occasionally, thyroid neoplasms including papillary thyroid carcinoma are detected incidentally in thyroidectomy specimens operated for non-neoplastic diseases like goitre. Hence histopathology is considered as the gold standard in the diagnosis of these diseases. The proposed study is intended to further establish the role of histopathological study along with its correlation with clinical, biochemical and radiological parameters in the diagnosis of HT.

MATERIALS AND METHODS

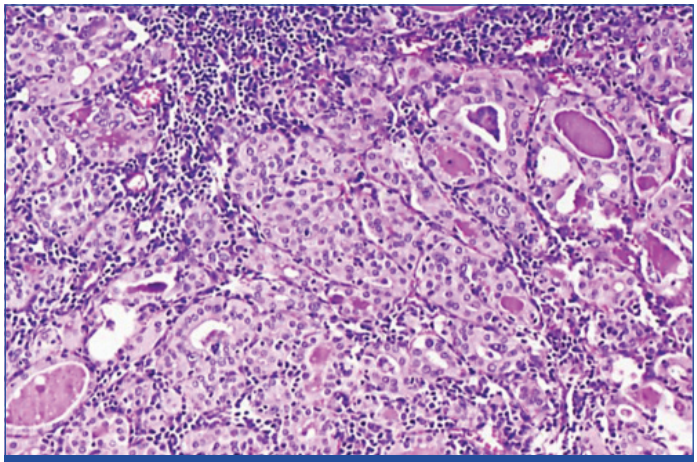
A retrospective study was conducted on thyroidectomy specimens of patients with HT in a tertiary care hospital over a period of five years i.e., January 2011 to December 2015.

Fifty five thyroidectomy specimens comprised of material for this study [Table/Fig-1]. These specimens were capt in 10% formalin solution. After representative sections were obtained paraffin embedding was done. Sections of five micron thickness were cut and stained with Haematoxylin and Eosin (H&E). The number of slides reviewed per case ranged from 2-10. Relevant clinical information, immunological, biochemical, radiological findings and follow-up details were recorded from medical records of the patients and results were analysed. Patients without HT were excluded. The study protocol was approved by the Ethical Committee of the hospital (451/2015). The total triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (thyrotropin or TSH) levels were measured by Electrochemiluminescence Immunoassay (ECLIA) method. The values of 0.6-2.02 ng/mL, 5.13-14.06 µg/dL and 0.27-5.5 µ IU/mL were considered to be in normal range for T3, T4 and TSH, respectively. Anti-TPO and anti-Tg titres measured by ECLIA method. Anti-TPO values >34 IU/mL and anti-Tg values >115 IU/mL were considered as positive.

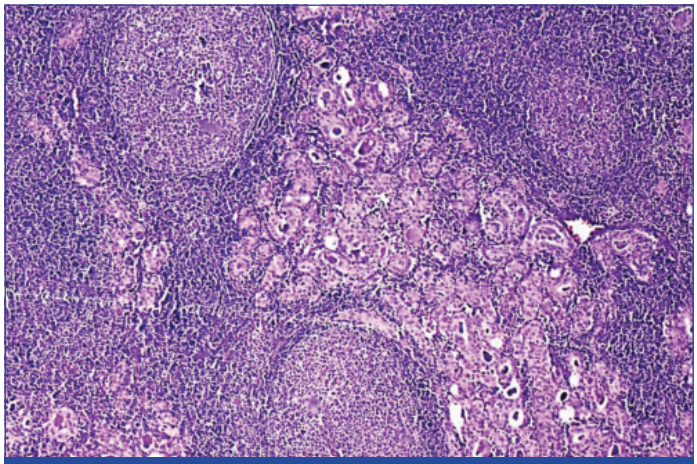


[Table/Fig-1]: Diffuse symmetric enlargement of the thyroid gland with homogenous fish-flesh grey tan cut surface.

All cases diagnosed as HT during the study period were thoroughly studied and reclassified into two groups; cases with characteristic hurthle cell change in a background of lymphoplasmacytic infiltrate and lymphoid follicles were categorised as HT while those without or with focal hurthle cell change in a similar background were grouped under Chronic Lymphocytic Thyroiditis (CLT) [Table/Fig-2-6]. Additional findings including malignancies, non-neoplastic nodules and incidental microscopic findings were also documented. The morphological findings were subsequently correlated with the available biochemical and radiological findings.



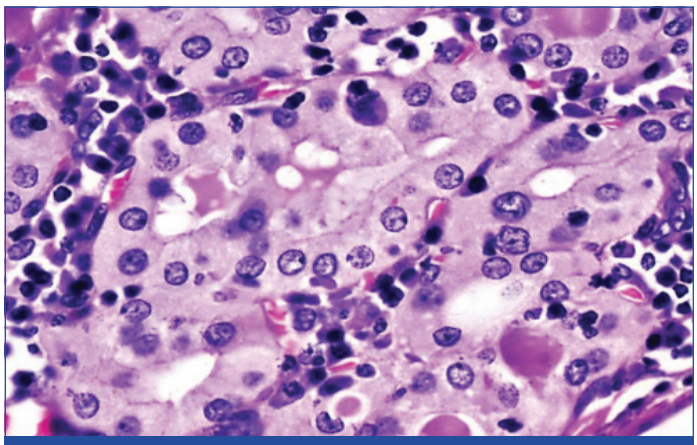
[Table/Fig-2]: Atrophic follicle surrounded by lymphoplasmacytic infiltrate in HT (H&E x 100).



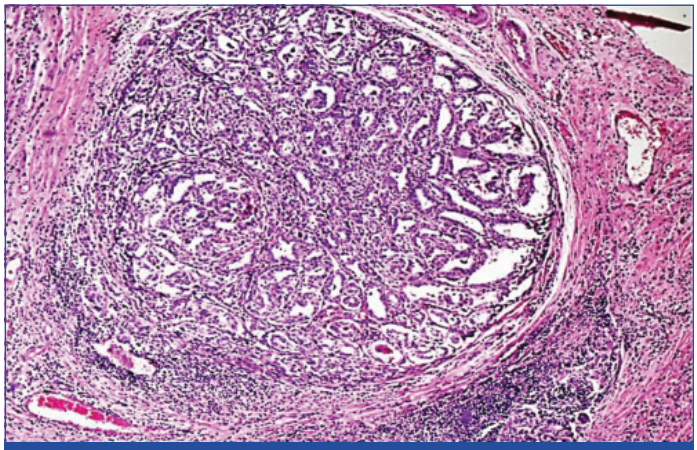
[Table/Fig-3]: Lymphoid follicles with active germinal centre in HT (H&E x 400).

STATISTICAL ANALYSIS

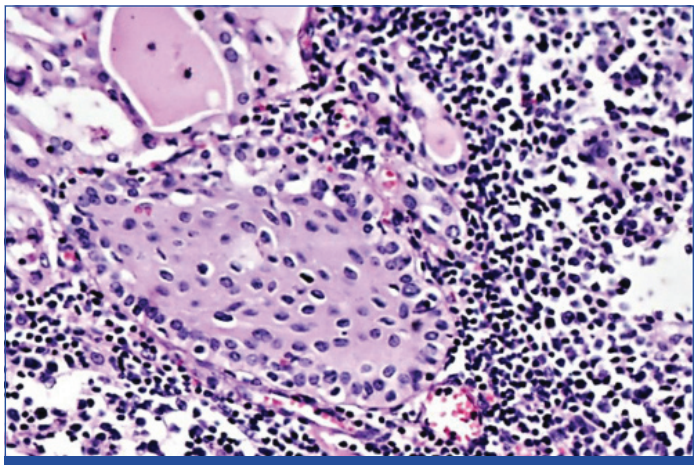
The thyroid hormone status, antithyroid antibodies and radiological parameters were correlated using the Fisher's-exact test where applicable. A p-value of ≤0.05 was considered statistically significant. For statistical analysis, IBM SPSS 20.0 data software was used.



[Table/Fig-4]: Follicles lined by hurthle cells: large polygonal cells with abundant granular eosinophilic cytoplasm and nuclear pleomorphism (H&E x 400).



[Table/Fig-5]: Papillary carcinoma thyroid in a background of HT (H&E x 40).



[Table/Fig-6]: Ultimobranchial body remnant seen as an incidental finding in HT (H&E x 200).

RESULTS

A total of 55 patients with histopathology proven HT were included in the study. The histopathological slides were reviewed and reclassified into two groups based on hurthle cell change. Thus, 35 cases were diagnosed as HT while the remaining were categorised as CLT. The age range of patients with thyroiditis ranged from 21 to 69 years with a median of 42 years. In HT, most of the patients (63%) belonged to the age group 30-50 years while only 8% were older than 60-years of age. Similarly, majority of patients with CLT were in the age group of 40-50 years. Both forms of thyroiditis were identified in younger age groups. An amount of 34 (97.1%) of 35 patients with HT were women. Similarly, 90% of patients with CLT were women. In other words, a marked female preponderance was seen [Table/Fig-7].

Age (Years)	21-30	31-40	41-50	51-60	>60
HT (N=35) (%)	5 (14.2%)	11 (31.4%)	11 (31.4%)	5 (14.2%)	3 (8.5%)
CLT (N=20) (%)	3 (15%)	3 (15%)	9 (45%)	4 (20%)	1 (5%)
Gender	**Male**	**Female**			
HT (N=35) (%)	1 (2.9%)	34 (97.1%)			
CLT (N=20) (%)	2 (10%)	18 (90%)			
Clinical presentation	**Midline neck swelling**	**Both pain and swelling**	**Compressive symptoms**		
HT (N=35) (%)	31 (88.6%)	3 (8.6%)	7 (20%)		
CLT (N=20) (%)	19 (95%)	1 (5%)	3 (15%)		
Thyroid hormone status	**Euthyroid**	**Subclinical hypothyroidism**	**Overt hypothyroidism**	**Hyperthyroidism**	
HT (N=33) (%)	11 (33.3%)	14 (42.4%)	6 (18%)	2 (6%)	
CLT (N=18) (%)	11 (61%)	4 (22%)	2 (11%)	1 (5.5%)	

[Table/Fig-7]: Clinical findings in HT and CLT.

Most patients with both forms of thyroiditis presented with chief complaints of midline neck swelling followed by compressive symptoms [Table/Fig-7]. Pain, lump and swelling were less common complaints. The duration of thyroid swelling ranged from one month to 18 years with most of the cases presented with thyroid swelling within two years duration.

T3, T4 and TSH levels were available in 33 cases of HT and 18 cases of CLT. T3&T4 was found normal in 28 and 25 cases of HT, respectively. TSH was elevated in 20 (66.6%) cases and normal in 11 (33%) cases. Elevated TSH level was recorded in 6 (33.3%) CLT cases and normal in 11 (61%) cases. In other words, most cases of HT had subclinical (42.4%) or overt hypothyroidism (18%) at the time of initial presentation while most cases of chronic lymphocytic thyroiditis were euthyroid [Table/Fig-7].

In the present study, ultrasound examination was performed in 21 cases of HT and 15 cases of CLT. There was a significant overlap in the ultrasound findings of the two types of thyroiditis. In both groups, echogenicity on ultrasound varied considerably from hypoechoic to mixed. The thyroid gland was hypoechoic in most cases regardless of thyroiditis subgroup. Presence of well-defined margins was also noted in both forms of thyroiditis. Other features documented on ultrasound include intranodular vascularity, halo, and microcalcification [Table/Fig-8]. The thyroid gland was noted to be hypoechoic in 57% of HT. Further, microcalcification and halo were noted in 14.2% and 19% cases, respectively. Presence of intranodular vascularity was documented in 14 of 21 cases (66.7%). Similarly, the thyroid gland was hypoechoic in 60% of the cases of chronic lymphocytic thyroiditis. Microcalcification and halo were seen in 46.6% and 6.7% cases, respectively. Intranodular vascularity was present in ten of 15 cases (66.7%) of CLT [Table/Fig-8].

		HT (n=21) (%)	CLT (n=15) (%)
Echogenicity	Isoechoic	4 (19%)	1 (6.7%)
	Hypoechoic	12 (57%)	9 (60%)
	Hyperechoic	2 (9.5%)	1 (6.7%)
	Mixed	3(14.2%)	4 (26.6%)
Margins:	Well defined	11 (52%)	8 (53.3%)
	Ill-defined	3 (14%)	2 (13.3%)
Microcalcification		3 (14.2%)	7 (46.6%)
Halo		4 (19%)	1 (6.7%)
Intranodular vascularity		14 (66.7%)	10 (66.7%)
Anti-tpo antibodies (n=12)		**HT (n=9) (%)**	**CLT (n=3) (%)**
Positive		7 (77.8%)	2 (66.7%)
Negative		2 (22%)	1 (33%)
Anti-thyroglobulin antibodies (n=5)		**HT (n=2) (%)**	**CLT (n=3) (%)**
Positive		2 (100%)	2 (66.7%)
Negative		0	1 (33.3%)

[Table/Fig-8]: Ultrasonography findings and antithyroid antibodies in HT and CLT.

Echogenicity on USG was correlated with TSH in 20 cases of HT and 14 cases of CLT. In HT, 6 (65%) patients with hypoechoic thyroid had normal TSH value while 8 (72.2%) patients with reduced to mixed echogenicity had increased TSH value. By Fisher exact test this relationship was found to be significant. (i.e., p-value <0.05). However, this correlation was not found to be statistically significant (p-value 0.22) in case of CLT [Table/Fig-8].

Serum Anti-TPO was evaluated in nine cases of HT and three cases of CLT. Seven cases of HT and two CLT cases were positive for Anti-TPO, respectively all of these were female patients. Anti-thyroglobulin antibodies levels were evaluated in five cases i.e. two cases of HT and three cases of CLT. Both cases of HT and two cases of CLT had high titre of anti-thyroglobulin antibodies. Hence, there was no significant difference in the antithyroid antibody profile in both forms of thyroiditis [Table/Fig-8].

All 55 cases studied underwent total/subtotal thyroidectomy. Their pre-operative clinical diagnosis ranged from goitre (simple/MNG), solitary thyroid nodule, HT with suspected malignancy and compression symptoms.

The findings on gross examination of thyroid were recorded from histopathology report. The weight of the resected thyroid varied considerably, ranging from 5-260 gm. In both HT and CLT, all patients had increase in size and weight of the thyroid with an average size of 6 cm and weight of 42 gm, respectively. Eighty eight percent cases of HT showed diffuse thyroid enlargement, some with lobulation and 62.8% cases with ill-defined nodularity [Table/Fig-9].

	HT (n=35) (%)	CLT (n=20) (%)
1. Diffuse enlargement	31 (88.5%)	15 (75%)
a) Lobulation	17 (48.6%)	4 (20%)
b) Nodularity	22 (62.85)	13 (65%)
c) Both lobulation and nodularity	10 (28.5%)	2 (10%)
2. Solitary thyroid nodule	4 (11.4%)	2 (10%)

[Table/Fig-9]: Gross morphologic features of thyroid in HT and CLT (N=55).

In the present study, based on light microscopic examination all cases were reclassified into two groups i.e., Chronic Lymphocytic Thyroiditis (CLT) and Hashimoto Thyroidis (HT) [Table/Fig-10]. All cases of HT and CLT showed classic features of lymphoid infiltrate arranged in lymphoid follicles with interfollicular small round lymphocytes and plasma cells [Table/Fig-2]. On microscopy, most lymphoid follicles had well-defined germinal centre surrounded by mantle zone [Table/Fig-3]. Hurthle cell metaplasia was a constant feature in all cases of HT [Table/Fig-4], while it was either absent or focally present in chronic lymphocytic thyroiditis. Further, the presence of follicular atrophy was a common feature of HT and less often seen in CLT. However, there was no significant difference in the extent of stromal fibrosis and presence of colloid in the two groups [Table/Fig-3]. Other incidental findings identified included solid cell nest or ultimobranchial body remnant consisted of small

	HT (n=35) (%)	CLT (n=20) (%)
Epithelial		
Follicular atrophy	19 (54.3%)	6 (30%)
Hurthle cells	35 (100%)	0
Squamous/epidermoid metaplasia	1 (2.9%)	0
Stroma		
Lymphoplasmacytic infilterate	35 (100%)	20 (100%)
Lymphoid follicles	35 (100%)	20 (100%)
Stromal fibrosis	8 (22.9%)	6 (30%)
Other features		
Hurthle cell nodule	13 (37.1%)	4 (20%)
Hurthle cell adenoma	0	1 (5%)
Incidental findings		
Ultimobranchial body remnant	1 (2.9%)	0
Associated malignancies		
Papillary carcinoma/microcarcinoma	3 (8.6%)	9 (45%)
Other carcinoma	0	2 (10%)

[Table/Fig-10]: Microscopic features of HT and CLT.

nests of polygonal cells and scant stroma located in the interfollicular interstitium [Table/Fig-6].

Hurthle cell nodules are benign lesions consisting of nodules of oncocytic follicular cells was seen in 13 of the 35 cases (37.1%) of HT and 4 out of 20 cases (20%) of chronic lymphocytic thyroiditis. Hurthle cell neoplasm is composed predominantly of hurthle cells forming around 75% or more of the tumour. The majority of these tumours are benign with complete encapsulation and are labelled as Hurthle cell adenomas. In the current study, one case of Hurthle cell adenoma was seen in a background of chronic lymphocytic thyroiditis [Table/Fig-10].

An amount of 3 out of 35 cases (8.6%) of HT also harboured neoplasm i.e., papillary thyroid carcinoma that had a characteristic papillary growth pattern with delicate central fibrovascular core and nuclear features of PTC [Table/Fig-5] while nine cases of CLT has concomitant papillary thyroid carcinoma of which one case is of oncocytic variant of PTC and two shows incidental detection of papillary microcarcinoma. Recurrence on follow-up was seen in 2 out of 9 cases of CLT with papillary thyroid carcinoma and cervical lymph node metastasis is seen in 5 out of 9 cases (55.6%). Other differentiated thyroid malignancies encountered include one case each of follicular and Hurthle cell carcinoma respectively in a background of CLT [Table/Fig-10]. Both the cases were on regular follow-up and free of complications.

Follow-up: The duration of follow-up ranged from 0-60 months, with a mean of 11 months. Five patients of HT and seven patients of CLT were lost to follow-up, while most of the patients were on follow-up for around 12 months. Post-operative complications reported included transient hypocalcaemia, post-operative stridor and Bell's palsy which subsequently improved. All patients were given thyroxine supplement therapy during follow-up and were clinically euthyroid with and follow-up at an interval of 2-3 months. Patients who had papillary thyroid carcinoma in addition underwent radioactive iodine scan and therapy for residual malignancy/recurrence and subsequently achieve remission. One of the patient with oncocytic variant of papillary thyroid carcinoma in a background of HT developed lung metastasis subsequently.

DISCUSSION

HT is an organ specific autoimmune condition characterised by destruction of thyroid follicles. Incidence of HT seems to be increasing. It has become 10 times more common than it was until the early 1990s. The increase in the incidence has been linked to excess iodine intake, particularly in coastal areas [6,7].

It is important to diagnose HT, as patients subsequently become hypothyroid and require lifelong thyroxine supplementation. Also, there is an increased risk of thyroid malignancies and extranodal marginal lymphoma in patients with HT, which emphasises the need for long term follow-up.

In the present study, HT was diagnosed in a wide age group ranging from 21 to 69 years with a mean age of 42.47 years; a majority of the cases, (63%) were in the age group of 30-50 years, which is similar to the findings of various other authors [8-11].

Autoimmune thyroid diseases consistently have a strong female preponderance [13]. This finding has been documented by various authors [7,10,14]. Further, this female preponderance is also noted in chronic lymphocytic thyroiditis with a male to female ratio of 1:9.

In the present study, most of the patients presented with the chief complaint of swelling (97.2%) in anterior neck. Other complaints include compressive symptoms (dyspnea, dysphagia) while few patients presented with both pain and thyroid swelling. The present findings are similar to those documented by Purnaiah M and Rakesh G and Lekha BS et al., [10,14]. However, compressive symptoms were more frequently documented in the present study. In the present study, the majority (42%) of patients presented with thyroid swelling within two years. Similar findings have been reported by various authors [11,14].

In the current series, all cases underwent subtotal (42%) or total (58%) thyroidectomy. Their pre-operative clinical diagnoses included multinodular goitre (68.5%), diffuse goitre (11%) and less frequently solitary thyroid nodule. Similar findings have been noted by other authors [7,10,14].

In the present study, 60.5% of patients with HT were hypothyroid while 33.4% were euthyroid and remaining 6% hyperthyroid. These findings are comparable with those of other authors [7,8,10,14]. In the present study, anti-TPO evaluation was performed in nine patients of HT and levels were raised in seven of them (77.8%). Lekha BS et al., documented 80% of the patients with high level of anti-TPO antibodies [14]. This included 30% of patients with high titre of anti-TPO alone while 50% of patients with high titre for both anti-TPO and anti-Tg. Similar findings have also been reported by other Indian authors [7,10].

In the present study, diffuse thyroid hypoechogenicity and increased vascularity were seen in 57% and 66.7% of the cases respectively. These findings are in concordance with the study findings of Marcocci C et al., [15]. However, other authors have noted that these findings are not specific for thyroiditis [16]. Pedersen OM et al., reported that 78% patients with final diagnosis of HT had reduced echogenicity on thyroid ultrasonography [17]. They made the conclusion that hypoechogenicity of thyroid gland is a strong indicator of autoimmune thyroiditis even when not clinically suspected. The present authors noted a higher percentage of hypoechoic lesions in the present study also.

Thyroid function was correlated with degree of echogenicity in both groups i.e., HT and CLT patients. Hypothyroidism was noted in 53.3% HT patients with reduced to mixed echogenicity, which is slightly lower when compared with the findings documented by Marcocci C et al., where 63.6% of patients with reduced echogenicity were hypothyroid [15]. These studies suggested that diffuse hypoechogenicity is indicative of diffuse autoimmune pathogenesis of the thyroid gland and predicts the development of hypothyroidism. Other findings like well-defined thyroid margins and halo have also been documented in other series [18].

In the present study, the most frequent indication for surgery in both HT and CLT was enlargement of thyroid gland in the form of either multinodular goitre or solitary thyroid nodule. These findings are in concordance with those of Amani HK [19]. In both forms of thyroiditis in the present study, all patients had increased size and weight of the thyroid gland which is similar to the study was done by other authors [19-21].

In the present study, all cases of HT showed classic pathological features. The most striking feature seen at low power is lymphocytic infiltration of thyroid gland. They organise into lymphoid follicles with germinal centres, like compartmentalisation seen in lymph nodes and spleen. Interstitium showed the infiltration mainly by lymphocytes, along with plasma cells and few macrophages, conferring a pale and grey-tan colour to the cut surface. Another feature seen in the interstitium is stromal fibrosis. Hurthle cell metaplasia was a constant feature in all cases of HT while chronic lymphocytic thyroiditis differed from HT because of the focal nature of hurthle cell change with less prominent lymphocytic infiltration and lack of germinal centre. Similar findings have been documented in other series [19,21-23].

In the present study, squamous metaplasia was rare and seen in only one of 35 cases (2.9%) of HT. Apel RL et al., reported that chronic thyroiditis may act as a trigger for squamous metaplasia and enlargement of these metaplastic foci resulting in the formation of squamous epithelial lined cysts [24].

Similarly, incidental finding of ultimobranchial body remnant referred to as solid cell nests consist of small nests of polygonal cells with ovoid nuclei and often pale finely distributed chromatin was seen in one case (2.9%) of HT. Li Y et al., have reported the occurrence of solid cell nest/squamous metaplasia in 12 of 105 cases (11%) of HT and more often in IG4-thyroiditis compared to non IG4 forms [20]. Similarly, Harach HR et al., reported solid cell nest in 32.5% of thyroid glands examined in fetal autopsies and 89% of neonatal autopsies [25].

Neoplasms most commonly seen in association with HT were PTC and primary thyroid lymphoma. Various studies published to signify the relationship between the two. They highlight the two to three times increased risk of PTC in the background of HT and vice versa also seen with 1.9 times higher rate of HT seen in association with HT. The clinical presence of dominant nodule, less response to suppressive therapy and presence of metastasis increases the suspicion of PTC in patients of HT. Various study on prognosis of HT in PTC shows the protective role of autoimmunity in terms of less aggressive disease at presentation, low recurrence [26] and improved survival [27].

Limitation(s)

This study is vulnerable to biases of retrospective analysis due to small cohort, incomplete data availability and variation in clinical management. Also, the present study was conducted in a tertiary centre, the composition of patients in the study may not be comparable to the general population.

CONCLUSION(S)

Hashimoto's thyroiditis (HT) was diagnosed in patients clinically presented as goitre from iodine sufficient western coastal area. The patients presented clinically as goitre and hypothyroidism point towards the need for further evaluation of the disease. USG further complement the diagnosis but histological features were confirmatory. Also, overlapping clinical, biochemical, radiological and morphological features of two forms of thyroiditis, it is observed that they are part of same spectrum and not two distinct entity. Association of HT with malignancy requires a close follow-up of these patients.

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