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Incidence and types of thyroid tumor in chronic lymphocytic thyroiditis

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ABSTRACT

The Chronic Lymphocytic Thyroiditis (CLT) is the most common inflammatory disorder that affects the thyroid gland. It presents either as goitrous (hashimoto thyroiditis) or Atrophic Thyroiditis (AT) and the only difference between them is the presence of goiter that detects by clinical examination. The diagnosis are confirmed by hormonal profile of high TSH with normal or low T3, T4, high autoantibodies or by FNCA preoperatively .The histopathology in HT is diagnostic. The management is medical, but if the disease is presented with goiter, the surgical interference is indicated in case of the pressure effect or malignant changes. The commonest malignant tumor of thyroid gland is the Papillary Thyroid Carcinoma (PTC) 80%. Follicular carcinoma occurs in 10% of cases. Lymphoma is rare malignancy of thyroid gland but certainly complicates CLT. The association of HT and PTC is still topic of debate since first described in 1955.

Material and Methods: Retrospective study aims to determine the malignant changes in CLT, especially the PTC by analysis of 900 thyroidectomy operations that were undertaken in Diwaniyai hospital from 2014 - 2019 . All the cases are diagnosed postoperatively by histopathology. The patients are divided into two age group, group A between 20-40 years and group B above 40 years

Results: The study revealed 81 cases with HT, all of them were presented to the surgeons because of un-diagnostic goiter that did not investigate by autoantibodies or by FNCA. 21(25%) patients of them show malignant changes. PTC is seen 16 cases (20%) of HT, while 4 cases with lymphoma and only one case with follicular carcinoma. In group A that includes 38 patients, 13 of them are with PTC. In group B that include 43 patients , 3 of them with PTC

The study also include analysis of 156 cases with differentiated thyroid carcinoma (DTC), 142 of them are PTC. In the analysis of histopathology of 156 cases with DTC, HT is seen in 17 cases while no case shows the histopathology of atrophic thyroiditis. 7 cases of PTC (44%) are microscopic . 8 cases (50%) are multifocal . 15 (88%) of DTC are seen in females and 2 (12%) in males

5 patients of 8 male patients with HT are complicated by malignancy, 3 of them are with lymphoma.

Key words: chronic lymphocytic , patients, tumor

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INTRODUCTION

Chronic Lymphocytic Thyroiditis (CLT) is the commonest inflammatory disease of thyroid gland and it is most common in female at the menopause , but any age may be affected [1].The female to the male ratio is 10-20 to 1 [2].The disease presents with different thyroid volumes between two extremes, goitrous (hashimoto thyroiditis) and atrophic form, and there are no accurate characters to differentiate between them. They differ only in the presence or absence of goiter that are detected by clinical examination [3]. In goitrous type , the enlargement of thyroid gland is from mild to moderate [2]. In most cases of HT, the gland is 40 g, two or three times of normal size but may be any weight between mild enlargement and 350 g [3]. The goiter may be diffuse or localized to one lobe, nodular, with different consistency, but in classical presentation the goiter is diffuse, firm, lobulated [2]. In 20% presented with hypothyroidism and 5% with thyrotoxicosis [2]. however hypothyroidism is inevitable event that may occur rapidly or extremely slowly.

Investigation: 1- hormonal profile mainly in form of high TSH with low or normal T3 and T4. 2-Autoantibodies are increased (high Thyroid Peroxidase (TPO) in 95% and anti-thyroglobulin in 60%) [2]. the most appropriate investigation is fine needle cytology aspiration (FNCA) which show lymphocytes infiltration. CLT is histological diagnosis that is characterized in goitrous type by diffuse lymphocytic infiltration, may be with germinal centre. The thyroid follicles are small sizes containing less colloid and fibrosis. The follicle is lining with hurthles cells. if the finding is only

lymphocytes infiltration,the diagnosis needs thyroid antibodies in atrophic type, the thyroid is small with lymphocytic infiltration and the follicles are replacing by fibrous tissue [3].The histopathology of HT is not changing and second biopsy that were done 20 years latter show little histological changes so no evidence that goitrous forms end in atrophic type [4].

HT is certainly complicated by primary thyroid lymphoma and recent studies indicate primary lymphoma may evolve from HT although this accident is rare [5].

Surgery is done occasionally on basis of suspicion of malignancy or for goiter causing pressure effect or for cosmetic cause.

The thyroid neoplasm is either in form of benign tumor (follicular adenoma) or malignancy that either arises from follicular cells, mainly Differentiated Thyroid Carcinoma(DTC) in 90-95% and undifferentiated type or that arise from C – cell (medullary carcinoma) . DTC is either Papillary Thyroid Carcinoma (PTC) in 85% of cases or follicular carcinoma. PCT-RET is the most frequent oncogene seen in PTC. BA is implicated as a cause of PTC [6].

The DTC carries good prognosis which mainly covered by size of tumor, age of the patient at diagnosis and the presence of metastasis [6].

The link between HT and PTC was subject of many studies, in spite of that the debate is still open since first described in 1955 [7].

MATERIALS AND METHODS

The study is retrospective and includes 81 patients with HT that present to the surgeons because of un-diagnostic goiter. The patients has not been investigated preoperatively by autoantibodies or Fine Needle Cytology Aspiration (FNCA)and no case was diagnosed as HT preoperatively . All the cases were diagnosed as HT postoperatively by histopathology that show small thyroid follicles that are lined by hurthle cells of variable sizes with diffuse lymphocytes infiltration which form lymphoid follicles that showing secondary germinal centres occasionally .According to the age ,the patients with HT are divided in two groups ,group A between 20 to 40 years and includes 38 patients and group B between 41 to 65 years and includes 43 patients.

The 81 patients with HT are subgroup of 900 cases of thyroidectomy operations that were undertaken in the teaching al-Diwaniyai hospital from 2014-2019. The analysis of these 900 cases also show 156 patients with DTC and the study also shows the incidence of HT in DTC and compare their characters with DTC without HT.

Total thyroidectomy are done in 57 cases of HT while the remaining were undertaken lobectomy.

All cases with lymphoma were undertaken total thyroidectomy except one case was operated by right lobectomy.

The HT were divided according to its size of goiter into group of small size, the longest dimension is 5.5 cm that include 23 patients. The second group, the longest dimension is more than 5.5cm.

RESULTS

Of 900 patients who underwent thyroid operations in our hospital for 6 years, 81 cases were diagnosed with HT according to histopathological findings. Of patients with HT, the numbers of females are 73 and the number of male are 8.
21(26%) cases of patients with HT show malignant changes in the thyroid gland and only one with follicular adenoma. The commonest type of malignancy is papillary carcinoma 16 cases (76%) , 7 of them (44%) cases are micro papillary . 8 cases (50%) of PTC are with multifocal lesions. Of those patients suffering of HT, 38(46.9%) patients are between 20 to 40 years old and 13(34.2%) patients of them were associated with DTC while the other 43(53%) patients are between 41 to 65 years and only 4(9.3%) of them were associated with DTC. One case of PTC in HT is oncocytic variant of PTC. 4 cases(19%) of 21 cases with malignancy are complicated by lymphoma(non-Hodgkin – B-cells) and three of them are males in age of 20 years, 39 years, 55 years and only one is female 55 years old .
15(88%) cases of DTC in HT are females and only two (12%) are males. One case of HT is

female with follicular carcinoma One case of HT has associated with adenoma.

The DTC in 8 cases (50%) are developed in small size goiter of HT. 23 patients (28%) of HT are presented as small size goiter.

The analysis also shows 156 cases with DTC and 17(10.9%) cases of them are HT. 142 of DTC are PTC and 16 cases of them (11.2%) are HT, and 14 cases of DTC are follicular carcinoma and only case is HT (Table 1 and 2).

Tab. 1. The associated tumor with HT

Total number	No associated pathology	Papillary thyroid carcinoma	Follicular thyroid carcinoma	Lymphoma non-hoghkin B cell	adenoma
Female patients 73	56	14	1	1	1
Male patients 8	3	2	-------	3	-------
Total patients 81	59	16	1	4	1

Tab. 2. The associated tumor in HT according to the age

Number of patients with HT.	Papillary thyroid carcinoma	Follicular thyroid carcinoma	lymphoma	adenoma	Total numbers of the associated tumor.
Group A (38 cases) Between 20-40 years	13 (34.2%)	1	2	1	17 (44.7%)
Group B (43 cases) Between 41-65 years	3 (9.6%)	-----	2	----------	5 (11.6%)
Total number 81 cases	16 (19.7%)	1	4	1	22(27%)

(Table 3). shows the high-level resistance against many antibiotics in the present study may be as a result of both intrinsic and acquired mechanisms. This resistance is widespread and constitutes serious clinical threats.

Tab. 3. Show the characters of PTC in HT in compare with PTC in non HT

PATHOLOGY	Total number	Female	Age 20-40 years	Microscopic	multifocality
PTC in HT	16	14(87.5%)	12 (75 %)	7 (43.75%)	8 (50%)
PTC in non-HT	126	82 (65%)	67 (53 %)	27 (21%0	32 (25%)

The aim of the study is to determine the relation between HT and thyroid neoplasms and its implications in surgical practice by retrospective analysis of 900 cases who were undertaken thyroidectomy operations for goiter in our institute between 2014-2019.

The analysis of thyroidectomy operations revealed 81 cases with HT. In the evaluation of this subgroup for associated pathology, the results are 22 cases (27%) associated with neoplasms, 21 cases of HT (26%) are malignant, 16 cases (20%) of HT are papillary thyroid cancer, 4 cases of HT (5%) are lymphoma, and one case is follicular thyroid carcinoma and only one case with follicular adenoma.

The link between HT and PTC was subject of many studies, in spite of that the debate is still open since first description of this relation in 1955 [7].

The finding of high incidence of PTC in our study, 16 case (19.7%) of 81 with HT , is established by many studies (Table 4). in analysis of the study by Yun Zhang et.ai that include 839 patients with HT, a high incidence of PTC was found(29.4%) [8]. Other study that are done by C. include 47 patients who underwent total thyroidectomy for pre-operative diagnosis of HT. 13 patients (27.6%) of them, the histopathology prove a diagnosis of PTC. The same study also show the prevalence of HT in PTC which was 19(26.7%) of 71 who underwent surgery for PTC [9]. 63 (29%)of 217 patients with HT had PTC and female patients with HT undergoing thyroidectomy are 30% more likely to have PTC [10].

In their study found that 163 patients of pre -operative diagnosis of HT shows 51(31.3%) cases have presented with differentiated carcinoma , 47 of them are papillary type ,3 of them are follicular carcinoma . In 126 cases with PTC, 36 cases show the histo pathological feature of HT [11].

HT is more predictor for PTC in compare with other risk factors [12].

The incidence of incidental thyroid cancer is increased significantly in cases with HT, there were 43 (7.4%) among 580 patients who did thyroidectomy [13].

Retrospective cohort study that were done included 452 HT patients, PTC was diagnosed in 106(23.5%) patients [14]. the highest incidence is seen from area of high prevalence of HT which show 381(58.3%) of PTC in 653 patients with HT [15].

So the coexistence of PTC in HT are proved by many surgical series in different areas of the world.

To avoid the selection bias in the above surgical series, the study that was done on thyroid nodules with positive serum anti-thyroid globulin supports this significant association between PTC and HT [16]. In our study ,there is no preoperative diagnosis of HT and the operations were done on all cases of un-diagnostic goiter even if they are small sizes so the effect of selection bias that are seen in the surgical series with preoperative diagnosis of HT is diminished and this may explain the least rank of association between PTC and HT that are seen in our study relative to the surgical series .

In 12 (75%) of 16 patients with PTC in HT, the disease occur in early adult life before 40 years and only four patients between 41 -65 years . The finding of high incidence of PTC in the younger age of HT patients is supported by other studies.

Because the bulk of PTC in HT occur before 40 years, while the bulk of HT occurs at menopause, according to that we adjusted the already high incidence of DTC in HT [21%] according to the age. With this adjustment, the incidence is further increased to be [36.8%] of HT before 40 years associated with DTC while the risk drops to 9.3% after 40 years. So every effort must be done for carful research of malignancy in HT, especially those of 40 years and younger, as one third of them is associated with DTC (Table 4).

Tab. 4. show some of surgical series with number and ratio of PTC in HT and number and ratio of HT in PTC

Name of study	Number of thyroidectomy	Number of Ht	Number and ratio of PTC in Ht	Number and ratio of Ht in Ptc
1-Coexistence of HT and PTC BY Zhang	8524	839	246 in 839 (29.4%)	246 in 1735(14.2 %)
2-coexistence of HT and PTC. Cipola		47	13 OF 47(27.6%)	19 of 71(26.7%)
3-Is HT a risk factor for PTC Daniel repplinger	1198	217	63 OF 217(29)	63 OF 293(21%)
4-Association between HT and PTC Gluseppa Graceffa	2175	214	51 of 163	36 of 142 (25%)
5-Coexistence of PTC In HT Aleksader K.	7545	452	106 of 452(23.5 %)	106 in 636 (16.6%)
6-The clinical feature of PTC in HT patients from an area of high prevalence of HT BY ZHANG L	6109	653	318 of 653(58,3 %)	318 of 2734 (11%)

The differentiated cancer in HT has its own clinical -pathology (Table 3). in addition to its high incidence in early adult life, other feature is the size of the malignancy which is smaller than in non HT and 7 cases(44%)

of 16 are microscopic size (less than 10 mm)in contrast with 27 (21%)PTC in non HT. Of 17 cases with DTC, 15(88%) cases are female and in contrast to DTC in non HT which show 82(65%) of cases are females.

Multi-focality was seen in 8 cases (50%) while only 32(25 %) of PTC in non HT are multifocal. These characters of PTC in HT are seen in other studies.

The age of the patient at diagnosis and the size of tumor in papillary or invasion of capsule in follicular carcinoma are the most important factors in the prognosis of differentiated thyroid cancer. These are indirect proofs of good prognosis of PTC in HT which are smaller in size and occur earlier.

The analysis of thyroidectomy also shows 142 case of PTC, 16(11.2%) cases of them with HT(to compare this finding with other study see the last vertical column in Table 4).

Although thyroid atrophy and goiter of CLT are not considered separate disorders and they are no more than two extremes of thyroid volume of the same disease, there is no reported case of DTC on the background of atrophic thyroiditis in contrast to 17 case of DTC on the background of 81 HT of goiter type. This is big difference between the two extremes of the same disease.

The autoimmune inflammation that ends with complete destruction of follicle cells, cells of origin, and its replacement by fibrous tissue that are seen in atrophic thyroiditis may explain this phenomena. So the destructive processes by autoimmune inflammation in atrophic thyroiditis is protective against DTC but in HT, the story is different.

More than one hypotheses try to explain this association between HT and PTC. The first one is high serum TSH. long exposure to high TSH in HT predispose the patient to PTC.

The second one is genetic.

RET/PTC the most frequent genetic alteration in PTC. Young age seems to be independent factor for the development of RET/PTC.

All patients with HT that not affect with PTC, as proved by histopathology, carry molecular evidence of thyroid malignancy. So these findings suggest multiple occult tumours exist in HT at high frequency and these findings make the HT at risk of malignancy because it is genetically predispose. BRAF mutation in HT can predict the development of papillary cancer in thyroid gland [17-21].

So the genetic material and high TSH in HT predispose to PTC as seen in our study of high incidence of PTC in HT if the autoimmune reaction do not completely destroy the follicle cells but if the autoimmune

Reaction is completely destroy the follicle cells as in atrophic thyroiditis, this will prevent development of PTC, as seen in our study of 'no reported case of PTC in atrophic thyroiditis", simply because of no available follicle cells. So the autoimmune inflammation and genetic material in HT are sometime counteracting effect regarding the risk of PTC.

The lymphoma is seen in 4 cases (5%) of 81 cases with hashimoto. All of them are non-Hodgkin B cell type. Lymphoma is well established complication of CLT but the incidence is very rare 0.1% mainly in older female above 50 years [22]. but in our study the incidence is 5% so it is not uncommon and 3 of them are males and 3 of them occur before 40 years.

One case of PTC in HT is oncocytic type. Most of oncocytic variety of PTC is associated with HT [23].

The ratio of male to female in HT is 1 to 10-20, in our study 8 cases are male of total 81 cases. 5 cases (62%) of 8 cases are associated with malignancy in form of PTC and lymphoma although the size of sample is small but this finding of high malignant rate in male with HT is significant.

CONCLUSION

Malignant changes are common complications in the patients with HT and one quarter of them are associated with DTC and lymphoma. The PTC is the most common malignancy in HT and occurs in

19% of HT, this ratio is further increased if adjusted with age that is 40 years or younger; to be one third of HT between 20-40 years are complicated by PTC. The PTC in HT has its own clinical and pathological feature in comparison with PTC in non- HT which are earlier age, more common in female gender, smaller size, and multifocality. The lymphoma is in the second rank, 5%. While only one case (1.2%) is with follicular carcinoma. So every effort must be done to follow patients with HT for malignant changes especially if presented in early adult life.

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