Thyroiditis in Mosul: a clinico-pathological study

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ABSTRACT

Objective: To estimate the relative frequency, as well as specific pathological features of thyroiditis in thyroidectomy specimens in Mosul.

Methods: One hundred (100) cases of histopathologically proved thyroiditis had been evaluated between July 2001 and March 2002. Histopathological examination , serum autoantibody assay, with thyroglobulin immuno-histochemical marker were done. In addition we utilized results of thyroid function tests brought by many patients

Results: Hashimoto's thyroiditis (H.T), 31 cases, F:M ratio 30:1, median age 38 years. Eighty percent of the cases were euthyroid. Focal lymphocytic thyroiditis (FLT) was recognized in 66 cases. It was divided into three grades according to the intensity of the lymphocytic infiltration, all cases showed female preponderance with F:M ratios of 9:1, 23:1 and 1:1 for grades I,II and III respectively with a mean age of 37 years. H.T. and FLT shared positivity for serum autoantibody and the presence of other pathological conditions of the thyroid, namely follicular adenoma, Hurthle cell(H.C.) adenoma and papillary carcinoma. Immunohistochemical stain for thyroglobulin monoclonal antibody marker showed strong reactivity within the atrophic follicles in H.T..The remaining three cases include granulomatous, suppurative and Riedel's types of thyroiditis.

Conclusions: Thyroiditis is a common condition in Mosul with marked female preponderance, and incidence in adulthood. The two main types encountered were H.T and FLT . Hashimoto's thyroiditis invariably shows Hürthle cell metaplasia either in focal or diffuse pattern of growth, particularly the latter. While H.C., if present, are mainly sporadic in FLT. In H.T., thyroid function is related to the type of follicular epithelial cells and the presence or absence of plasma cells.

الخلاصة:

أجريت هذه الدراسة في مدينة الموصل خلال فترة ثمانية أشهر (تموز ٢٠٠١إلى آذار ٢٠٠٢) ثم حددت خلالها مائة حالة التهاب في الغدة الدرقية تم فصلها من ٢٩٨ نموذج استئصال للغدة الدرقية وقد مثلت نسبة الالتهاب حوالي ٣٣,٥% من مجموع الحالات الكلي. لقد أجريت دراسة مكثفة للحالات المائة اعتمادا على الفحوص السريرية والمرضية وتحديد الحالة الوظيفية للغدة الدرقية وكذلك فحوصات إضافية شملت وجود الأجسام المضادة في مصل الدم، كذلك فحوصات مناعية كيمياوية ونسيجية على المقاطع النسيجية.

بصورة عامة الإناث أكثر عرضة للإصابة من الذكور بنسبة (١١,٥ إلى ١) وبمتوسط عمري هو ٣٥ سنة لكلا الجنسين. التهاب الغدة الدرقية نوع (هاشيموتو) تم تشخيصه في ٣١ حالة ونسبة الإناث إلى الذكور (٣٠ إلى ١) ومتوسط العمر كان ٣٨سنة. وظائف الغدة الدرقية كانت طبيعية في ٨٠% من هذه الحالات عند الفحص السريري والمختبري. بعد إجراء الفحص النسيجي تبين أن هناك تغير في نوع الخلايا الطبيعية المبطنة للجرابات الموجودة في الغدة الدرقية وكذلك زيادة في تخلل خلايا اللمف والبلازما في الأنسجة وكذلك وجود أو عدم وجود خلايا البلازما. أما في حالة الالتهاب اللمفي البؤري للغدة الدرقية فقد مثل نسبة ٦٦% من حالات الالتهاب وقد تم تصنيفها إلى ثلاثة مراتب حسب كثافة الخلايا اللمفية. لقد وجد

أن هناك غلبة الإناث على الذكور فيما يتعلق بنسبة الإصابة بالمرض وحسب الصنف (٩ إلى ١) و (٢٣ إلى ١) و (١ إلى ١) بالنسبة إلى صنف ١و٢و٣ على التوالي. وقد كان متوسط عمر الإصابة هو ٣٧ عاما. بالإضافة إلى النوعين السابقين من الالتهاب، فقد تم تشخيص ثلاث حالات إضافية من أنواع أخرى هي نوع (التهاب الغدة الدرقية تحت الحاد والالتهاب التقيحي والالتهاب من نوع ريدل) وذلك على شكل حالة واحدة لكل نوع.
التهاب الغدة الدرقية بنوعية هاشيموتو والبؤري اشتركا بوجود نتيجة ايجابية للفحوص المناعية على مصل الدم كذلك وجود حالات مرضية مرافقة لكلا النوعين من الالتهاب وهي أورام حميدة وورم خبيث.
لقد تبين أيضا وجود زيادة في التفاعل الموجود في المقاطع النسيجية عند إجراء الفحص المناعي الكيمياوي النسيجي على هذه المقاطع خاصة في حالة التهاب هاشيموتو ولكن لم يمثل هذا التفاعل خصوصية لهذا النوع من الالتهاب.

Thyroiditis encompasses a group of disorders that includes not only the process of clear cut inflammatory nature, but also lesions of uncertain significance, in which sclerosis and lymphocytic infiltrates are the most relevant pathologic findings[1]. Traditionally it embraces the following types:-

1. Acute thyroiditis (infectious and non infectious thyroiditides)
2. Subacute thyroiditis (DeQuervain's or granulomatous thyroiditis) ,manifested with multinucleated colloid containing intrafollicular giant cells.
3. Other granulomatous inflammations; which include; palpation thyroiditis; tuberculosis; sarcoidosis; mycoses; postoperative necrotizing granuloma, histiocytic granulomatous inflammation around haemorrhage; granulomatus vasculitis; syphilis; malakoplakia; and intrathyroidal dendritic cells, epithelioid cells and giant cells in Iodine deficient goitre.
4. Autoimmune thyroiditis: it includes; Hashimoto's thyroiditis(Hurthle cell metaplasia, germinal lymphoid follicles and fibrosis; focal lymphocytic thyroiditis; atrophic thyroiditis; juvenile chronic lymphocytic thyroiditis; postpartum thyroiditis; and painless or silent thyroiditis.
5. Riedel's thyroiditis, microscopically presented as extensively hyalinized fibrous tissue completely replaces the area of the gland involved[2-6].

The major objectives of this study are to find out the relative frequency of thyroiditis in thyroidectomy specimens in Mosul, the age and gender distribution of cases with thyroiditis, the specific pathological features of various types of thyroiditis, as well as the clinicopathological correlation of thyroiditis utilizing additional methods of investigations.

Patients and Methods

A prospective study was performed during an eight months period from July 2001 – March 2002; thyroidectomy or lobectomy was performed on 298 patients presented with goitre to the surgical departments of Al-(Jamhory) Teaching Hospital, Salam General Hospital and AL-Zahrawi Private Hospital in Mosul city.

The patients comprised 264 women and 34 men with a mean age of 34 years (age range from 15 to 60 years). One hundred (100) cases of histopathologically proved thyroiditis were segregated for this study. Those included 92 females and 8 males with a mean age of 35 years.

For a selected number of cases, the following tests were performed:-

I. Qualitative assay of circulating thyroid autoantibodies (anti-Tg and anti-TPO) in 39 patients, AMA and ANA for 35 patients . The tested sera were from patients with thyroid disorders in general, and carried out by using special kits and ELISA. The degree of lymphocytic infiltration in FLT, was graded 1-3 according to the number of lymphocytic foci[2,7].

II. Immunohistochemical technique:

Avidin–biotin peroxidase complex immunohistochemical technique was available in limited amount that allowed performing it in 12 cases of thyroiditis only, using deparaffinized sections for the detection of thyroglobulin antigen by utilizing thyroglobulin monoclonal antibody marker.

III. Thyroid function tests were available preoperatively for 35 cases (35%), which include serum T3 T4, and TSH concentrations.

Results:

Table(1) summarizes the histologic types of thyroiditis and their gender distribution.

Table(2) demonstrates the associated conditions recognized in 5 cases of H.T. (16%) and 11 cases of FLT (16%).

Clinico pathological correlation of thyroiditis;

Hashimoto's thyroiditis: **Table(3)** demonstrates the correlation between the different histological parameters adopted in this study and the function of the thyroid as stated clinically or by hormonal assays.

Subacute (granulomatous) thyroiditis ,Riedel's thyroiditis, suppurative thyroiditis :One case of each of these types was identified (table1).

Laboratory findings

Thyroid function tests**;**

Assessment of T3, T4 and TSH was carried out preoperatively on 35 cases of thyroiditis irrespective of the specific type. The results show 37% euthyroid, 57% hyperthyroid, and 6% hypothyroid.

Serum autoantibody titers were qualitatively assessed by ELISA technique. Nine cases of the tested sera from 17 patients with proved FLT, have positive anti-Tg (53%), 13 cases (76%) have positive anti-Tpo, 3 cases (17%) have positive AMA, and a single case (6%) of the total 17 cases was positive for ANA. Four cases of H.T were tested by this assay and showed positive anti- Tg, anti – Tpo each in two cases. A single case was positive for anti- Tg, anti – Tpo, ANA and AMA.

Immunohistochemical technique;

For the first twelve cases of thyroiditis only, thyroglobulin monoclonal antibody marker was tested; they comprised 7 cases of H.T. and 5 cases of FLT . Strong immunoreactivity was identified in the follicular cells and Hürthle cells lining the atrophic follicles mainly in H.T., while in FLT, the staining was uniformly negative.

Figures (1-6) demonstrate gross and microscopical features of types of thyroiditis.

Table (1): Histopathological types of thyroiditis according to gender.

Type	Number %	Female	Male
Hashimoto's thyroiditis	31	30	1
Focal lymphocytic thyroiditis			
Grade I	40	36	4
Grade II	24	23	1
Grade III	2	1	1
Subacute thyroiditis	1	1	
Riedel's thyroiditis	1	1	
Suppurative thyroiditis	1		1
Total	100	92	8

Table (2) : Pathological conditions associated with different types of thyroiditis.

Type	Follicular adenoma	H.C. Tumor	Papillary Ca.
- Hashimoto's thyroiditis 5/31 (16 %)	1 (3%)	3 (10%)	1 (3%)
- Focal lymphocytic thyroiditis 11/66 (16 %)	6 (9%)	4 (6%)	1 (1.5%)
Grade I	4	1	
Grade II	1	3	1
Grade III	1		

Table (3): Hashimoto's thyroiditis; comparative results of histopathological parameters and function (30 females and one male).

Histologic parameter	No. and %	Euthyroid	hyperthyroid	P. value
1. lymphoid follicles				
with germinal centre	22(71%)	17(77%)	5(23%)	N.S.
without germinal centre	9(29%)	7(77.7%)	2(22.2%)	
2. Hürthlecell metaplasia				
Diffuse	13(42%)	8(62%)	5(38%)	N.S.
Focal	18(58%)	16(89%)	2(11%)	
3. Fibrosis				
Mild	15(48%)	12(80%)	3(20%)	
Moderate	12(39%)	9(75%)	3(25%)	N.S.
severe	3(10%)	2(66.6%)	1(33.4%)	
absent	1(3%)	1		
4. Thyroid follicles				
of nontoxic type	23(74%)	21(91%)	2(9%)	N.S.
of toxic type	4(13%)	1(25%)	3(75%)	
mixed	4(13%)	2(50%)	2(50%)	
5. Atrophic follicles				
Present	31(100%)	24(77.5%)	7(22.5%)	N.S.
Absent				
6. Plasma cells				
Present	21(68%)	20(95%)	1(5%)	< 0.05
Absent	10(32%)	4(40%)	6(60%)	
7. Giant cells				
Present	2(6%)	2		N.S.
Absent	29(94%)	22(76%)	7(24%)	

Table (4): Positive results of the qualitative assessment of serum autoantibody titer in patients with thyroiditis (Number of patients and percentages are in parenthesis).

Serum autoantibody type	FLT grade I(8)	FLT grade II(8)	FLT grade III(1)	FLT Total	H.T. (4)
Anti – Tg	2 (25%)	7 (88%)	0	53%	2
Anti – Tpo	4(50%)	8(100%)	1	76.5%	2
AMA	1(17%)	2(25%)	0	17.5%	1
ANA	0	1(12.5%)	0	6%	2

Figure (1)(Left) Cut surface of a gland involved by diffuse variant of Hashimoto's thyroiditis (vaguely nodular surface).
Figure (2)(Right) Riedel's thyroiditis, non lobulated diffuse fibrotic cut surface with loss of normal thyroid appearance.

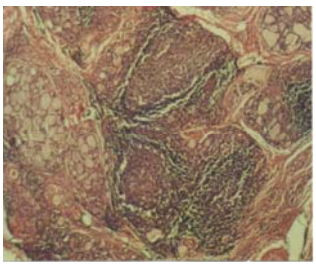
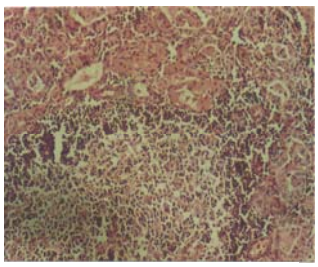

Figure (3)(Left) Hashimoto's thyroiditis, multiple germinal lymphoid follicles, bands of fibrous septa, and nontoxic colloid follicles (H&E X 20).
Figure (4)(Right) Hürthle cell metaplasia lining atrophic follicles in close proximity to a lymphoid follicle with germinal centre in a case of H.T. (H&E X 40).

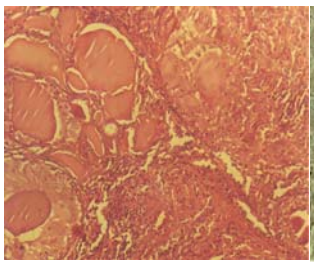
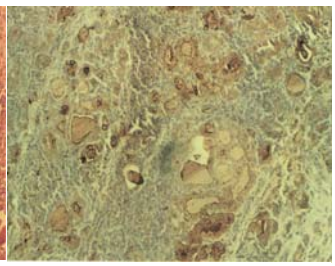

Figure (5)(Left) Granulomatous thyroiditis with colloid containing giant cells (H&E X40).
Figure (6)(Right) Strong immunoreactivity for thyroglobulin in cells lining atrophic follicles in a case of Hashimoto's thyroiditis (immunoperoxidase stain X40) .

Discussion:

By using strict and well defined diagnostic criteria during a one year period, we tried to identify and analyse the frequency and the significance of thyroiditis amongest 298 thyroidectomy specimens performed in Mosul city; a locality which is endemic with goitre.

Unspecified thyroiditis was observed in 33.5% of the cases, which is close to results reported by others; namely (40% Carcangiu and DeLellis 96[1]; 30% Moosa and Mozzaferri 98[6]; and 26% Livolsi 94[2]).

In thyroiditis, female predominance is pronounced with a F:M ratio of 11.5:1. Similar observation has been reported by others[1,7-11]. The mean age was 35 years. Similar age incidences were observed by other authors[1,7,8,10,11].

Hashimoto's thyroiditis

Thirty one cases with H.T. were seen in this study, accounted for 10.4% of all thyroid disorders in Mosul. This frequency is close to or similar to the ratio observed by others as demonstrated in the comparative table below;

The condition predominates in females with F:M ratio of 30:1; This is consistent with another study[2]. The mean age is 38 years, similar to age distribution as described by others[1,2,3,6]. Clinically, the majority of the patients (80%) were euthyroid at presentation. This is similar to the findings observed by others[1,2,3,6,11-15], and is consistent with the usual clinical course of H.T. where thyroid function progresses from overactive to normal and ending up in hypothyroid state[1,2,3]. Grossly thyroidectomy specimens had the patterns expected in H.T.[1-3,6,13], which were either nodular and fibrosing (64%) or diffuse (36%). Sporadic cases show additional features including: follicular adenoma (one case), H.C. adenoma (three cases) and papillary carcinoma in a single case. Follicular adenoma is a lesion common to the thyroid and can be seen in association with every type of thyroid disorders[16]. The latter two conditions might be considered as complications of H.T.[3,17,18] or incidental findings.

Thyroid disorder	Mossa and Mozzaferri 98[6]	Gardiner and Russell 95[8]	McKee et al 95[9]	Thanoon 93[10]	Current study
H.T.	10%	4%	6%	7%	10.4%

Microscopically:

Thyroid follicular cells, were of the nontoxic simple type in 74% and normal function in 92%, or of the toxic hyperplastic type with thin absorbed colloid, which was directly related to the function of the thyroid as assessed by TFT. Thus, in 75% of cases with toxic goitre, the follicular cells were either of the toxic or the mixed type.

Hürthle cells, diffuse H.C. change was observed in 42% of the cases. In the rest, it was multifocal (58%). Hyperthyroidism was observed in 38% of those with diffuse H.C. change, so it is possible, that change from focal to diffuse follows the progression of the disease[1-4], although the concordance between the degree of metaplasia and the function is not total and the majority of patients were euthyroid (77.5%) with P- value > 0.05. All cases of H.T. have small atrophic follicles, often lined by Hürthle cells, the majority of these cases (77.5%) have normal thyroid function, this was similar to that recognized by others[1,2]. However, the number of the thyroid follicles (whether toxic, nontoxic, or mixed) decreased among the remaining atrophic follicles[1,3].

The fibrosing variant of H.T. was observed in 3 cases (10%). This type shows accentuated fibrosis and is seen in 10-12% of cases of H.T. as described by others[1,3]. There was no obvious correlation with the function as 2 out of 3 cases were euthyroid (p value >0.05).The degree of lymphocytic infiltration was variable. However in 71% of the cases, it was intense with germinal centres. Similar observation was made by others[3,6,13,19]. No significant correlation was noticed between the lymphocytic infiltration and the thyroid function since 74.5% of the cases were euthyroid.

Plasma cells, were identified in 21 cases (71%), recognized mainly in fibrosing variant as stated in previous studies[1,3]. Giant cells; are sparse in H.T. and in this study were observed in 2 cases only, both of which were euthyroid. These cells are known to occur in intrafollicular location [3,20].

Focal lymphocytic thyroiditis:

It forms 22% of all thyroid disorders in this study, It is within the ratio of 22-40% and a female preponderance (F:M ratio of 10-20:1) as recognized by others[1,2,3,6,21,22].

The age incidence was 30-50 years with a mean age of 37 years. There is no apparent significant relationship between the degree of lymphocytic infiltration and the age incidence as noticed also by Mitchell and Kirkham 84[21].

Thyroid function tests were available for 28 out of 66 cases of FLT, 15 (53%) were hyperthyroid, 11 (39%) were euthyroid and the remaining two cases (7.3%) were hypothyroid. Similar variation in thyroid function has been described by others[1,7,22].

Microscopically

Follicular cells, are predominantly of the simple nontoxic type with abundant colloid . This feature was matched by euthyroid in 62% of the cases with an exception of 2 cases with grade III whose thyroid function showed overactivity irrespective of the follicular lining by simple (nontoxic) epithelium. Foci of Hürthle cells were noticed in 6 cases, most of which were euthyroid . Similar observation was made by others[3,19,22].

Atrophic follicles were seen in 42% of the cases of grade II and III, but in only 4% of grade I which is similar to the results made by Greenberg et al 70[22]. However, statistical analysis of the correlation between the type of the follicular epithelium and the thyroid function was not significant (P value > 0.05).

Fibrosis was scanty in 57.6% of the cases. A single case of grade I showed marked degree of fibrosis and was also euthyroid. A similar case with severe fibrosis has been reported by Greenberg et al 70[22] from a collection of 30 cases.

Lymphocytic infiltration, was categorized into 3 grades according to its intensity[2]. In the majority of cases, lymphoid aggregates devoid of germinal centres are the main type, particularly in grades I and II (98% and 71% respectively). However germinal centres were observed in the remainder and were abundant in grade III. Rosai 96[3] and Livolsi and Merino 81[19] also described similar results.

Plasma cells, were absent from the inflammatory infiltrate in 88% of the cases. This was unlike the infiltrate in H.T. which invariably contains a number of plasma cells, it

appears that the immunological response is more intense in H.T. than in FLT, although hypothyroidism is likely to occur in the latter following thyroidectomy[3,7].

Antibodies in thyroiditis:

Qualitative assessment of serum anti-Tg and anti- Tpo was available for only 4 patients with H.T. The results show equal distribution for positivity with 2 cases in each category viz; anti-Tg and anti-Tpo. The number is too small to be of any significance, however studies on larger scales had shown variable results for each of the 2 antibodies as illustrated in the table below:

Study	Anti- Tg	Anti –Tpo
Walter and Tulbot 96[23]	45%	90%
Dayan and Daniels 96 [24]	60%	95%
Estienne et al 99[25] (437 cases of H.T.)	40%	40%
Zophel et al 99[26] (36 cases of H.T.)	61%	61%
Current study (4 cases)	50%	50%

As for FLT, the number of cases assessed was more (17cases) but includes all grades of lymphocytic infiltrates. Anti-Tg was positive in about half of the cases (53%) while Anti-Tpo was positive in almost 2/3rd of them (76.5%). Patients with grade II FLT show 100% positivity for Anti-Tpo, while only 50% of patients with grade I were positive for the same test. Again ,the number of cases is of little calibre to be of definitive significance, however, it does support the suggestion made by others[1,3,6], that FLT may have an autoimmune pathogenetic mechanism with a good and definite correlation between the degree of lymphocytic infiltration and the titre of Anti –Tpo[27] and as illustrated below:

Study	No. of patients	Anti-Tg	Anti-Tpo
Tanner et al 82[28]	63	36.5%	95%
Grubeck et al 86[29]	20	35%	50%
Zophel et al 99 [26]	28	64%	64%
Current study	17	53%	76.5%

Antimitochondrial antibody, was assessed in the sera of the same group of patients above. The titer was positive in 1/4 cases of H.T. and 3/17 cases of FLT. This antibody is shared with other autoimmune conditions specifically primary biliary cirrhosis[30,31] and the two conditions are known to coexist [32,33].Antinuclear antibody, was positive in 2/4 cases of H.T. and 1/17 cases of FLT which was of grade II. It has been recognized that patients in whom ANA is positive, tend to express Anti-Tpo more frequently than in those with negative ANA[34]. Shibasaki et al 90[35] and Sato et al 99[36], reported a single case, each of H.T. associated with primary biliary cirrhosis in whom the ANA and AMA were positive. In our group of 4 patients with H.T. assessed for AMA and ANA, a single case was positive for both. However, the patient was not clinically known to have any features of cirrhosis.

In summary and irrespective of the small number of cases, the presence of autoantibody in over half of the cases of H.T. and FLT tested, is concordant with the concept of autoimmune pathogenesis for both diseases[1,23,37].

Immunohistochemical staining for thyroglobulin, expressed strong positive reaction mainly in the atrophic follicles which are lined mainly by Hürthle cells. This is concordant with the observation made by Carcangiu and DeLellis 96[1]. However, considering the high cost of this technique, it can hardly be recommended as a marker for H.T.

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