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CLINICOPATHOLOGICAL EVALUATION OF GOITER IN A SAMPLE OF IRAQI PATIENTS IN TIKRIT PROVINCE

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ABSTRACT

Background: Lesions of the thyroid gland are common around the world, albeit their prevalence and histological pattern vary by age group, gender, nutrition and environment. However; up to our knowledge, Histological description of goiter cases has not yet been studied in Tikrit Province, Iraq. **Aim of study:** To assess the histopathological findings of cases presented with goiter in a sample of Iraqi patients in Tikrit province and their correlation with clinicopathological parameters including (age, gender, thyroid status, and gross features of goiter). **Methods:** This is a cross sectional study that was conducted in Tikrit province. The cases involved were patients who presented with goiter that needed surgical resection. Assessment of histopathological diagnosis in relation to clinicopathological parameters was done. **Results:** A total number of 150 patients were included in the study. The mean age of the patients was 40.4 years ± 12.5, with most patients being of 20-39 years. The gender distribution showed a female predominance, as the female to male ratio was 10.5:1. multinodular goiter was the most common type (54.7%) among non-neoplastic lesions. Concerning benign neoplastic lesions, follicular adenoma was the most common (14.7%). As for malignant neoplasms, papillary carcinoma (intracystic, micropapillary, encapsulated) was the only type as it was detected in (8.0%). A statistically significant association was detected between histopathological diagnosis and both gross features and thyroid status, while No significant association was found between histopathology and neither age, gender. Moreover, no significant association was between thyroid status and thyroid malignancy. **Conclusion:** Non-neoplastic lesions constituted the majority of thyroid lesion with multinodular goiter being the most common. Concerning neoplastic lesion, follicular adenoma was the most common benign tumor; while papillary carcinoma was the only detected malignant neoplasm. The peak incidence was in the age group (20-29 years). Gender distribution showed overwhelming female predominance. A statistically significant association was detected between histopathological diagnosis and each of gross features, and thyroid status. Moreover, thyroid malignancy was significantly more common in female patients.

INTRODUCTION

Goiter is the most common manifestation of thyroid disease. Impairment in the production of thyroid hormone, most often brought on by a lack of dietary iodine, leads to the development of both diffuse and multinodular goiters. When the thyroid gland is unable to produce enough thyroid hormone, the body responds by increasing serum TSH, which in turn causes thyroid follicular cells to grow larger and multiply more rapidly. Extent of goiter correlates with severity and duration of thyroid hormone insufficiency. Multinodular goiter is produced by a combination of recurrent hyperplasia and involution.[1] Other causes of goiter include autoimmune diseases, benign, and malignant tumors.[2]

Thyroid adenoma is a benign tumor that arises from the gland's follicular epithelium. Although follicular adenomas are usually isolated, they are clinically difficult to be distinguished from a prominent nodule in a multinodular goiter; hence the need for a careful pathological assessment.[1]

Thyroid Hürthle cell adenoma, also known as a thyroid eosinophilic adenoma, is a rare benign thyroid tumor that often requires surgery but has a favorable prognosis after treatment. Preoperative diagnosis of Hürthle cell adenoma is challenging because of its low prevalence, absence of distinctive clinical signs, and lack of characteristic imaging findings. However, because to its distinctive histological characteristics, thyroid HCA may

be detected postoperatively by histopathological findings.[3]

Hashimoto thyroiditis is the leading cause of hypothyroidism in regions of the globe where iodine levels are adequate. It presents as painless thyroid swelling and is characterized by the gradual failure of the thyroid gland due to progressive autoimmune damage. The peak incidence occurs between the ages of 45 and 65, and the female to male ratio ranges from 10:1 to 20:1. Although more common in mature women, the illness may develop at any age, including in young children.[1]

Another cause of non-painful goiter is Riedel thyroiditis, which is a rare disease characterized by chronic inflammation and fibrosis of the thyroid gland. Classically, it presents as hypothyroidism with a "stone-like, hard-as-wood" non-tender thyroid gland.[4] Thyroid follicular cells are destroyed when thick fibrous tissue gradually replaces the thyroid parenchyma and adjacent structures. The fibrosis subsequently spreads to other nearby structures, including the airways, which in turn produces obstructive symptoms as dyspnea, dysphagia, and hoarseness.[5]

Subacute granulomatous (de Quervain) thyroiditis is characterized by painful goiter that is caused by an inflammatory process due to a preceding viral infection. The common symptoms are neck pain or discomfort, tenderness to palpation, and a predictable course of hyperthyroidism followed by euthyroidism, hypothyroidism, and back to euthyroidism.[6]

Concerning thyroid malignancy, it is the most frequent endocrine malignancy and the 5th most common cancer worldwide. According to the Iraqi global cancer observatory, thyroid cancer is the 5th most common cause of cancer Iraq, as 1660 cases were reported in 2020 representing 4.9% of all detected cancers.[7] classifies thyroid malignancy according to histopathology as The 2022 WHO update.[8] Follicular cell-derived malignant neoplasms: Differentiated tumors are usually curable with an excellent prognosis in early-stage disease; and hence, the importance of early screening and detection.[9]

Aim of study: To assess the histopathological findings of cases presented with goiter in a sample of Iraqi patients in Tikrit province and their correlation with clinicopathological parameters including (age, gender, thyroid status, and gross features of goiter).

MATERIALS AND METHODS

This is a cross sectional study that was conducted in Tikrit province at Al-Tawfiq Lab in the period from 1/1/2021-1/6/2022, i.e. one and a half year. The cases involved were patients who presented with goiter that needed surgical resection and were sent for histopathological examination to confirm the diagnosis. All patients who presented with thyroid enlargement and who consented to be a part of this study were included. A total number of 150 patients were included in the study. Data included age, gender, thyroid function test, size of lesion, gross appearance, and histopathological diagnosis were collected for patients pathology report. Hematoxylin and Eosin stain slides for all cases were collected and histopathological diagnoses were revised by an expert pathologist.

RESULTS

A total number of 150 patients were included in the study. The mean age of the patients was 40.4 years ± 12.5, with most patients being in the age group of 20-39 years. The gender distribution showed a female predominance, as the female to male ratio was 10.5:1. Female percentage was 91.3% and male percentage was 8.7%. Regarding the largest dimension of the goiter, the mean was 6.3 cm ± 1.3, with more than half (52.7%) being of 4-6 cm. Concerning gross features, solid cystic lesion was the most common feature (54.7%), followed by capsulated nodule (21.3%). As for thyroid status, the majority (78.7%) were euthyroid; as shown in tables (1&2). Regarding non-neoplastic lesions, multinodular goiter was the most common type (54.7%). Concerning benign neoplastic lesions, follicular adenoma was the most common (14.7%). As for malignant neoplasms, papillary carcinoma (intracystic, micropapillary, encapsulated) was the only type as it was detected in (8.0%).

Table 1: Age group distribution of the studied sample. Clinical characteristics, histopathological diagnosis of the studied sample.

Age group	**Frequency**	**Percentage**
<20 years	4	2.7
20-39 years	71	47.3
40-59 years	60	40.0
60-80 years	15	10.0
Total	150	100.0
Clinical characteristics	**Frequency (Total =150)**	**Percentage (%)**
Size (Total = 150)		
4-6 cm	60	45.8
6-8 cm	62	47.3
8-10 cm	8	6.1

10-13 cm	1	0.8
Gross features (Total = 150)		
Solid with cystic area	80	61.1
encapsulated nodule	32	24.4
Whitish area*	12	9.2
Solid grey	7	5.3
Thyroid status (Total = 150)		
Euthyroid	118	90.1
Hypothyroid	11	8.4
Hyperthyroid	2	1.5
Histopathology	**Frequency**	**Percentage**
Non-neoplastic. Total = 112 (74.6%)		
MNG	82	54.7
Hashimoto's thyroiditis	15	10.0
Lymphocytic thyroiditis	8	5.3
Grave's disease	4	2.7
Granulomatous thyroiditis	2	1.3
Riedel thyroiditis	1	0.7
Neoplastic (benign). Total = 26 (17.33%)		
Follicular adenoma in MNG	19	12.7
Hurthle cell adenoma in MNG	4	2.7
Follicular adenoma	3	2.0
Neoplastic (malignant) Total = 12 (8.0%)		
Papillary carcinoma	12	8.0
Overall total	**150**	**100.0**

*MNG: Multinodular goiter.*Whitish area can be single, multiple, or diffuse.

A statistically significant association was detected between histopathological diagnosis and both gross features and thyroid status, while No significant association was found between histopathology and neither age, gender. Moreover, no significant association was between thyroid status and thyroid malignancy. Relationship between gross features and histopathological diagnosis; significant association was detected between both parameters (p value < 0.001); as most cases with MNG showed solid cystic gross features, Follicular adenomas and Hurthle cell adenomas showed capsulated nodule, Hashimoto's thyroiditis showed solid grey appearance, most cases of papillary carcinomas showed whitish area, most cases of Grave's disease and lymphocytic thyroiditis showed solid grey morphology. Relationship between thyroid status and histopathological diagnosis, significant association was detected between both parameters (p value < 0.001); as all patients with Grave's disease had hyperthyroidism, while all other patients were hypothyroid and euthyroid (except for 2 (2.4%) cases of MNG who also were hyperthyroid.

Table 2: Relationship between age, gender and histopathological diagnosis (p value = 0.49).

Age	Histopathology										Total
	Multinodular goiter	**Follicular adenoma in MNG**	**Hurthle cell adenoma in MNG**	**Hashimoto's thyroiditis in MNG**	**Papillary carcinoma**	**Grave's disease**	**Lymphocytic thyroiditis**	**Granulomatous thyroiditis**	**Riedel thyroiditis**	**Follicular adenoma**	
<20 years	3	1	0	0	0	0	0	0	0	0	**4**
	3.7%	5.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**2.7%**
20-39 years	36	8	2	7	8	4	2	1	1	2	**71**
	43.9%	42.1%	50.0%	46.7%	66.7%	100.0%	25.0%	50.0%	100.0%	66.7%	**47.3%**
40-59 years	32	10	0	7	3	0	6	1	0	1	**60**
	39.0%	52.6%	0.0%	46.7%	25.0%	0.0%	75.0%	50.0%	0.0%	33.3%	**40.0%**
60-80 years	11	0	2	1	1	0	0	0	0	0	**15**
	13.4%	0.0%	50.0%	6.7%	8.3%	0.0%	0.0%	0.0%	0.0%	0.0%	**10.0%**
Total	**82**	**19**	**4**	**15**	**12**	**4**	**8**	**2**	**1**	**3**	**150**
	100.0%	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**

Gender	Histopathology										Total
	MNG	**Follicular adenoma in MNG**	**Hurthle cell adenoma in MNG**	**Hashimoto's thyroiditis in MNG**	**Papillary carcinoma**	**Grave's disease**	**Lymphocytic thyroiditis**	**Granulomatous thyroiditis**	**Riedel thyroiditis**	**Follicular adenoma**	
Male	6	2	0	1	3	0	0	1	0	0	**13**
	7.3%	10.5%	0.0%	6.7%	25.0%	0.0%	0.0%	50.0%	0.0%	0.0%	**8.7%**
Female	76	17	4	14	9	4	8	1	1	3	**137**
	92.7%	89.5%	100.0%	93.3%	75.0%	100.0%	100.0%	50.0%	100.0%	100.0%	**91.3%**
Total	**82**	**19**	**4**	**15**	**12**	**4**	**8**	**2**	**1**	**3**	**150**
	100.0%	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**

Gross features	Histopathology										Total
	MNG	**Follicular adenoma in MNG**	**Hurthle cell adenoma in MNG**	**Hashimoto's thyroiditis in MNG**	**Papillary carcinoma**	**Grave's disease**	**Lymphocytic thyroiditis**	**Granulomatous thyroiditis**	**Riedel thyroiditis**	**Follicular adenoma**	
Solid grey	0	0	0	14	0	3	7	0	0	0	**24**
	0.0%	0.0%	0.0%	93.3%	0.0%	75.0%	87.5%	0.0%	0.0%	0.0%	**16.0%**
Solid cystic	80	0	0	1	0	1	0	0	0	0	**82**
	97.6%	0.0%	0.0%	6.7%	0.0%	25.0%	0.0%	0.0%	0.0%	0.0%	**54.7%**
Capsulated	2	18	4	0	4	0	1	0	0	3	**32**

nodule	2.4%	94.7%	100.0%	0.0%	33.3%	0.0%	12.5%	0.0%	0.0%	100.0%	**21.3%**
Whitish area	0	1	0	0	8	0	0	2	1	0	**12**
	0.0%	5.3%	0.0%	0.0%	66.7%	0.0%	0.0%	100.0%	100.0%	0.0%	**8.0%**
Total	82	19	4	15	12	4	8	2	1	3	**150**
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	**100.0%**
Thyroid status	**Histopathology**										**Total**
	MNG	**Follicular adenoma in MNG**	**Hurthle cell adenoma in MNG**	**Hashimoto's thyroiditis in MNG**	**Papillary carcinoma**	**Grave's disease**	**Lymphocytic thyroiditis**	**Granulomatous thyroiditis**	**Riedel thyroiditis**	**Follicular adenoma**	
Euthyroid	80	19	4	0	12	0	0	0	0	3	**118**
	97.6%	100.0%	100.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	**78.7%**
Hypothyroid	0	0	0	15	0	0	8	2	1	0	**26**
	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%	100.0%	100.0%	0.0%	**17.3%**
Hyperthyroid	2	0	0	0	0	4	0	0	0	0	**6**
	2.4%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	**4.0%**
Total	**82**	**19**	**4**	**15**	**12**	**4**	**8**	**2**	**1**	**3**	**150**
	100.0%	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**

*MNG: Multinodular goiter.

Table (3): Relationship between age group and tumor (p value = 0.542), gender and malignancy (p value = 0.542), thyroid status and malignancy (p value = 0.218).

Age group	Malignancy		Total
	Benign	Malignant	
<20 years	4	0	4
	100.0%	0.0%	100.0%
20-39 years	63	8	71
	88.7%	11.3%	100.0%
40-59 years	57	3	60
	95.0%	5.0%	100.0%
60-80 years	14	1	15
	93.3%	6.7%	100.0%
Total	138	12	150
	92.0%	8.0%	100.0%
Gender	**Malignancy**		**Total**
	Benign	**Malignant**	
Male	10	3	13
	76.9%	23.1%	100.0%
Female	128	9	137
	93.4%	6.6%	100.0%
Total	138	12	150
	92.0%	8.0%	100.0%
Thyroid status	**Malignancy**		**Total**
	Benign	**Malignant**	
Euthyroid	106	12	118
	76.8%	100.0%	78.7%
Hypothyroid	26	0	26
	18.8%	0.0%	17.3%
Hyperthyroid	6	0	6
	4.3%	0.0%	4.0%
Total	138	12	150
	100.0%	100.0%	100.0%

Figure *1* : Papillary microcarcinoma: Section of thyroid gland from 45 year old female presented with goiter is showing encapsulated nodule(red arrow) with papillary architecture. (H and E ,4×).

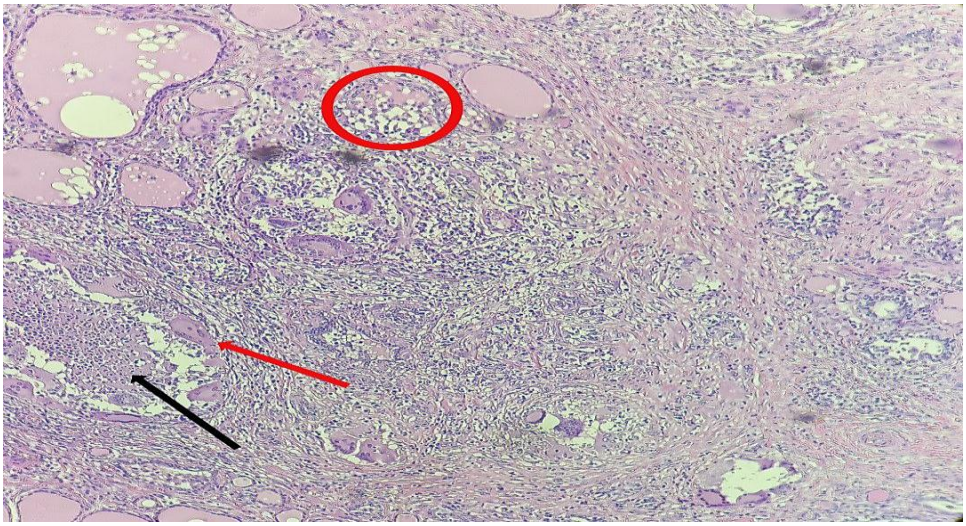

Figure (*2*): granulomatous thyroiditis: Section of thyroid gland from 39 year old female presented with goiter showing distrupted follicles(red circle) and heavy inflammation icluding multinucleated giant cells(red arrow) and foamy histeocytes(black arrow) with variable fibrosis.(H and E , 4x).

DISCUSSION

The mean age of thyroid disease in the current study was 40.4 years, and the peak incidence (47.3%) was seen in the age group (20-39 years). This is in concordance with the study by (Soloman et al., 2015) in Nigeria, the mean age was 36.3 years with the majority in the age group 30-39 years.[10] The present study showed an obvious female predominance, as the female to male ratio was 10.5:1, which is understandable since most thyroid lesions tend to show female preponderance.[11] Concerning other studies, (Soloman et al., 2015) in Nigeria, (Nzegwu et al., 2010) in Nigeria, and (Garalla et al., 2020) in Libya found female to male ratios of 6.4:1, 7:1, and 8:1; respectively.[10,12,13] Which is less than the gender gap pf the present study. In the current study, the frequency of neoplastic and nonneoplastic lesions is 25.3% and 74.6%; respectively. This is in exact concordance to the study by (Bukhari et al., 2015) in Pakistan in which neoplastic lesions constituted 25.5%.[14] However, (Qureshi et al., 2018) in Saudi Arabia found a lower frequency (18.0%).[15] Multinodular goiter(solid ,with cystic area and fibrosis) was the most common lesion, as it was detected in 120 (80%) cases either alone in 82 (54.7%) cases or associated with other findings in other 38 (25.4%) cases. This is in concordance with other studies, such as (Qureshi et al., 2015) in Saudi Arabia and (Alam et al., 2018) in Pakistan.[15,16] It is noteworthy to mention that most thyroid neoplasms present in multinodular goiter, suggesting that long standing MNG is a risk factor for thyroid cancer.[17] Hashimoto's thyroiditis(solid grey cut section) was the second most common non-neoplastic thyroid lesion, detected in 15 (10.0%) cases; of which 14 cases were females. This is also in concordance with (Qureshi et al., 2015) in Saudi Arabia and (Alam et al., 2018) in Pakistan. Moreover, both studies found cases of Hashimoto's thyroiditis that coexisted with papillary carcinoma,[15,16] which support the hypothesis that Hashimoto's thyroiditis is a risk factor for the papillary carcinoma development.[18] However, no such cases were found in the current study. Among benign neoplastic lesions, follicular adenoma(encapsulated nodule alone or in a background of multinodular goiter) was the most common constituting (14.7%) of the total cases and 84.6% of benign neoplasms, which is in agreement to the study by (Solomon et al., 2015) in Nigeria (15.7%), but higher than (Qureshi et al., 2015) in Saudi Arabia and (Alam et al., 2018) in Pakistan; who found frequencies of 6.2%, and 7.4%.[10,15,16] However, all the mentioned studies agreed that follicular adenoma was the most common benign neoplasm of the thyroid. Papillary carcinoma was(whitish area ,encapsulated nodule and cystic nodule) the only thyroid malignancy found in the current study (8.0% cases). Among 998 thyroid lesions studied by (Bukhari et al., 2020) in Pakistan, (15.3%) proved to be malignant. Papillary carcinoma was the most common malignancy (90.2%), followed by medullary carcinoma (4.2%) and follicular carcinoma (2.0%).[14] The absence of other types of thyroid malignancy in the present study can be attributed to its small sample size. A significant association was detected between gross features and histopathological diagnosis. A noticeable finding is that among 12 cases in which whitish area was found on the cut section, 8 cases were associated with papillary carcinoma. Another finding was that solid grey lesion was exclusively associated with either Grave's disease (still fleshy, but with small solid grey area), lymphocytic thyroiditis, or Hashimoto's thyroiditis. Thyroid malignancy showed a significant gender disparity as it was more common in female, which is consistent with the literature; Recent research on estrogen receptor status in thyroid cancer demonstrate a variation in the receptor subtypes expressed dependent on the histology of thyroid cancer, suggesting that reproductive factors may be to responsible for the female predominance.[19] Increased TSH concentrations have been linked to an increased risk of thyroid cancer in individuals with nodular thyroid disease in recent investigations. Furthermore, higher

TSH levels were associated with higher frequencies and more advanced stages of malignant tumors even when TSH levels were within the normal range.[20] As a result, some researchers have hypothesized that the development of thyroid autonomy can prevent the capability of mutated oncogenes to cause clinically detectable cancer by lowering TSH levels.[21] A study by (Fiore et al., 2009) in the United States concluded that patients who received treatment with levothyroxine to decrease serum TSH levels had a lower incidence of papillary thyroid malignancy (3.2%) than those who did not receive the treatment (5.1%).[21] In the present study, all cases of malignancy were observed in Euthyroid patients. However, the sample size was not large enough to draw a significant statistical inference. The study by (Cerci C et al., 2007) in Turkey obtained a malignancy incidence of 9% in toxic goiter and 10% in non-toxic goiter; However, their study included a small sample size.[22] Furthermore, a meta-analysis by (Negro R et al., 2013) could not find a significant association between TSH and incidence of thyroid carcinoma.[23] It is worth mentioning that (Elena et al., 2016) in Spain found that papillary carcinoma tends to be more aggressive in patients with hyperthyroidism than patients with normal thyroid status.[24]

CONCLUSION

Non-neoplastic lesions constituted the majority of thyroid lesion with multinodular goiter being the most common. Concerning neoplastic lesion, follicular adenoma was the most common benign tumor; while papillary carcinoma was the only detected malignant neoplasm. The peak incidence was in the age group (20-29 years). Gender distribution showed overwhelming female predominance. A statistically significant association was detected between histopathological diagnosis and each of gross features, and thyroid status. Moreover, thyroid malignancy was significantly more common in female patients.

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