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Evaluation of the Relationship between Various Histopathological Types of Primary Malignant Thyroid Carcinoma and Blood Groups

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Abstract

Background:

The ABO and Rh system have a great association to different kind of malignancy as mentioned in the literature. The data about prevalence of blood group with thyroid malignancies were limited in the literature; we aimed to record the relationship of different ABO and Rh blood groups with different malignant thyroid tumors.

Methodology:

the demographics, ABO blood group, Rh factor, histopathological type of malignant thyroid tumors were recorded for each patient with malignant thyroid tumor (MTT); then we evaluated the association between different blood group types with different histopathological pattern.

Results:

Papillary thyroid carcinoma (PTC) was the most common MTT [n=46, (92%)], while all other types were uncommon, they were follicular thyroid carcinoma [(n=1) 2%], medullary thyroid carcinoma [(n=1) 2%], Hurthle cell carcinoma [(n=1) 2%] and anaplastic thyroid carcinoma [(n=1) 2%]., the blood group A with Rh positive was the most frequent [n= 17, (34%)], , the O+ve was [n=15 (30%)], B+ve [n=10 (20%)], while AB-ve [n=3 (6%)] while a small number was Rhesus negative. The A+ve blood group was the commonest blood group in PTC patients (34.8%), followed by O+ve (30.4%).

Conclusion:

Blood group A+ve is the most frequently reported among cases of papillary thyroid carcinoma, which is the most common MTT.

Introduction

Thyroid malignant tumors are about 1% of the new diagnose malignant tumors (1). Men have low chance to affect by this disease and represent about 0.5% of men cancers and women have 1.5% are diagnosed by thyroid malignancy (1). All of the thyroid malignancies are carcinomas because all of them arise from thyroid epithelium (2). Two groups of thyroid carcinomas according to their differentiation are classified, which are differentiated and undifferentiated carcinoma (2).

At least 94% of thyroid carcinomas are differentiated and classified to papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and hurthle cell carcinoma (HCC), all differentiated thyroid carcinomas are derived from thyroid follicular epithelium. Another 5% are medullary thyroid carcinoma (MTC), which is a neuroendocrine tumor derived from the parafollicular or C-cell and the remaining 1% are anaplastic thyroid carcinoma (ATC) that derive from dedifferentiation of the differentiated type (2).

Blood type is determined by the presence or absence of particular antigens on the surface of red blood cells (3). According to some research, some diseases may be more common in people with particular blood types. It is crucial to remember that other factors, such as lifestyle, diet, and genetics, play a much bigger role in the majority of conditions than blood type alone does (4). The risk of developing certain digestive tract cancers, like stomach cancer, may be slightly elevated in people with blood type A (5). AB may be more susceptible to getting pancreatic cancer (6). Compared to other blood types, blood type O may have a slightly lower risk of developing blood clots and venous thromboembolism. An autoimmune disease called lupus has a slightly higher risk of developing in people with blood group B. It is significant to note that these associations are tentative, and additional research is required to fully comprehend the connection between blood types and disease risk (7). This study aimed to record the relationship of different ABO and Rh blood groups with different malignant thyroid tumors.

Materials and Methods

An approval from the scientific committee of the College of Health and Medical Technology / Sulaimani Polytechnique University was taken, and a signed informed consent or verbal acceptance was obtained from people who were participating in this study. This cross-sectional study enrolled 50 patients with primary malignant thyroid carcinoma. Patients who had proven through histopathological examination to have primary malignant thyroid tumor was included in this study. Any patients that did not meet the inclusion criteria of suspected patients based on the histological diagnosis were excluded from this study. The samples of this study were collected from Smart Health Tower / Sulaymaniyah city. The study extended from November 2021 to August 2022: the writing and analysis of the results were performed within the same period.

The age, sex, residency, occupation and histopathological examination of the patient's biopsy samples were evaluated. The ABO blood groups (A/B/AB/O) and Rh factor (positive vs. negative) were determined in the same time using hemaglutination method, and latest edition of American Joint on Committee on Cancer was used for Clinicopathological staging (8). The Statistical Package for Social Science (SPSS, Chicago, II, USA), version 26 was used for data entry and analysis. Numerical variables were summarized using medians and interquartile ranges (IQR) for skewed variables while mean and standard deviation was used for normal distributed data (9-12).

Results

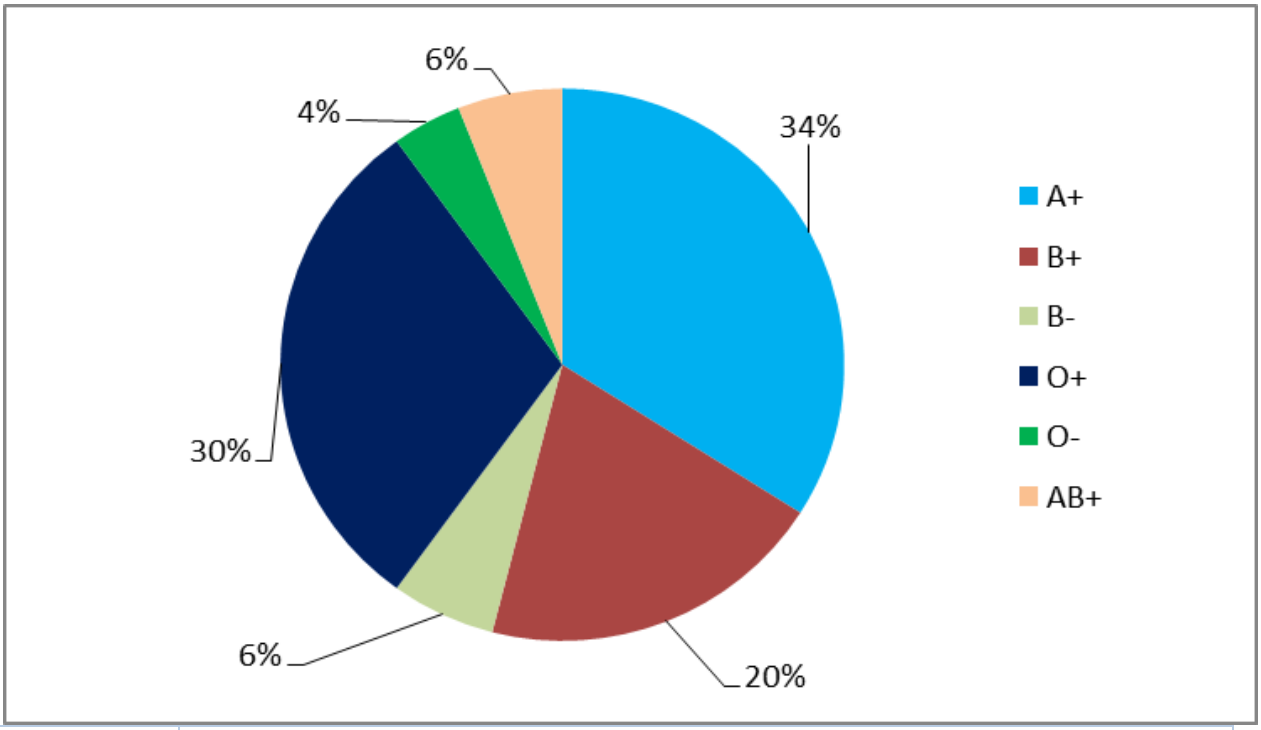
The study showed that most of the thyroid malignant patients were females (n= 35, 70%), the remaining 15 (30%) were males; the male to female ratio was (1:2.3) as shown in (table 4-1). Most of the patients were in age group 31- 50 years old (n=31, 62%). Most of patients were living in Sulaymaniyah city (n=17, 34%) followed by Hawler (n=10, 20%), (table 4-1). Housewife was the most occupation type among patients which was (n=29, 58%) followed by worker (n=11, 22%). The results revealed the presence of different primary malignant thyroid tumors, papillary thyroid carcinoma (n=46, 92%), follicular thyroid carcinoma (n=1, 2%), medullary thyroid carcinoma (n=1, 2%), Hurthle cell carcinoma (n=1, 2%) and anaplastic thyroid carcinoma (n=1, 2%).

Different blood groups were determined among patients. The four types of ABO blood group system were found among the study population; the blood group A with Rh positive was the most frequent (n= 17, 34%), the other blood groups were found in less frequency, blood group O with Rh positive was (n=15, 30%), B with Rh positive (n=10, 20%), and AB with Rh negative (n=3, 6%) while a small number was Rhesus negative. Furthermore, the frequency of the Rh-negative blood groups in patients was B (n=3, 6%), and O (n=2, 4%), (figure 4-1).

Table 4-1: Descriptive Statistics Of Patient Groups Regarding Gender, Age, Residency, And Occupation

Category	Patient Group=50 (%)
Gender	
Male	**15 (30)**
Female	**35 (70)**
Total	**50 (100)**
Age Group (Year)	
11-30	**9 (18)**
31-50	**31 (62)**
51-70	**7 (14)**
71+	**3 (6)**

Total	**50 (100)**
Mean ± S.D	**41.66 ± 14.07**
Residency	
Sulaymaniyah	**17 (34)**
Hawler	**10 (20)**
Other	**23 (46)**
Total	**50 (100)**
Occupation	
Housewife	**29 (58)**



Worker	**11 (22)**
Other	**10 (20)**
Total	**50 (100)**

Figure 4-1: Blood Group distribution among study population

Blood group A+ve was the most frequent blood group in PTC patients (34.8%), followed by O+ve

(30.4%) while blood groups regarding other thyroid cancers FTC, MTC, HCC and ATC were as follow: O+ve, O-ve, A+ve, and B-ve respectively, (table 4-2).

Table 4-2: Blood groups among different histological thyroid cancers in patients group					
Blood groups	PTC=46 (%)	FTC=1 (%	MTC=1 (%)	HCC=1 (%)	ATC=1 (%)
A+	16 (34.8)	0 (0)	0 (0)	1 (100)	0 (0)
B+	10 (21.7)	0 (0)	0 (0)	0 (0)	0 (0)
B-	2 (4.3)	0 (00	0 (0)	0 (0)	1 (100)
O+	14 (30.4)	1 (100)	0 (0)	0 (0)	0 (0)
O-	1 (2.2)	0 (0)	1 (100)	0 (0)	0 (0)
AB+	3 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)

The median (IQR) size of the PTC tumors was 1.35 (0.8-1.91) cm, while the sizes for other tumors were 1.5 cm for FTC, 5.5 cm for MTC, 6.5 cm for HCC, and 6 cm for ATC. 58.7% of PTCs were unifocal while the remaining 41.3% were multifocal; both FTC and HCC were unifocal while MTC was multifocal, (table 4-3).

Table 4-3: Size And Focality Of Different Malignant Thyroid Tumor

Tumor Type	Focality		Median Of Tumor Size (Cm) + (Iqr)
	Multifocal N (%)	Unifocal N (%)	
Ptc	19 (41.3)	27 (58.7)	1.35 + (0.8-1.9)
Ftc	0 (0)	1 (100)	1.50
Mtc	1 (100)	0 (0)	5.50
Hcc	0 (0)	1 (100)	6.50
Atc*	-	-	6
*Atc Not Records The Focality Because Incisional Biopsy Was Taken.			

In the current study, 16/50 was having lymph node metastasis; 30.43% of the PTC patients had lymph node metastasize, both FTC and HCC did not have metastasis while MTC and ATC cases have lymph node metastasize (table 4-4).

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Table 4-4: Metastasize Of The Thyroid Cancers The Patient Regarding		
Thyroid Cancers	Metastasize	No Metastasize
	N (%)	N (%)
PTC (N=46)	14 (30.43)	32 (69.57)
FTC (N=1)	0 (0.0)	1 (100)
MTC (N=1)	1 (100)	0 (0.0)
HCC (N=1)	0 (0.0)	1 (100)
ATC (N=1)	1 (100)	0 (0.0)

According to the AJCC staging system, the ATC was in the last stage IVB with pT4a N1 M0, the HCC was at first stage with pT3a NX MX**,** the FTC in stage I with pT1b N0, while MTC was in stage III with pT3a N1a Mx. Only 2.2% of PTCs were in stage II with pT3a N1a, and all remaining were in the first stage with different pathological staging as described in table (4-5).

Table 4-5: Clinicopathological Staging Of Malignant Thyroid Carcinomas According To American Joint Committee On Cancer (AJCC).		
Clinical Stage	**Pathological Stage***	**N (%)**
PTC=46		
I	**Pt1 N1b**	**1 (2.2)**
	Pt1a	**11 (23.9)**
	Pt1a N0	**6 (13.0)**
	Pt1a N1a	**1 (2.2)**
	Pt1a N1b	**1 (2.2)**
	Pt1b	**8 (17.4)**
	Pt1b N0	**4 (8.7)**
	Pt1b N1a	**1 (2.2)**
	Pt1b N1b	**3 (6.5)**
	Pt2	**2 (4.3)**
	Pt2 N0	**1 (2.2)**
	Pt2 N1b	**5 (10.9)**
	Pt3a N1a	**1 (2.2)**
II	**Pt3a N1a**	**1 (2.2)**
FTC=1		
*According To American Joint Committee On Cancer (AJCC) (8).		

Discussion

Cancer gender disparity in incidence, disease aggressiveness, and prognosis has been observed in a variety of cancers. In the current study, the incidence of thyroid malignancies was 2.3 times more common in women than in men. Comparable findings were also observed by Jonklaas J, et al, and Rahbari R , et al. (13, 14) One of the possible explanations for female predominance in thyroid cancer is that females are more commonly affected by thyroid diseases than males especially in terms of autoimmune diseases which will provoke pathological changes that may contribute to malignant transformation. It has been hypothesized that reproductive, menstrual

and environmental factors may account for gender disparity in thyroid malignant tumor incidence (13, 14).

Sex hormones have a significant role in developing malignancy and are well documented for breast and prostate cancers. Hormone-specific nuclear receptors that control gene expression and tumor cell biology are the principle mechanism of sex hormones in cancer development (15). The α- and β-estrogen receptors mediate the effect of estrogen and are expressed in papillary thyroid cancer. Furthermore, estrogen can dramatically increase the rate of cell proliferation in thyroid cancer cell lines compared with male sex hormones (16, 17). The gender disparity in thyroid cancer is also specific to the histologic subtypes of thyroid cancer. This study revealed that three histological subtypes of thyroid malignancies (Medullary thyroid carcinoma, Follicular thyroid carcinoma, and Hurthle cell carcinoma) are only present in females; on the other hand, anaplastic thyroid carcinoma was present only in male.

Like the results of Ortega J, et al, and Chen AY, et al, the current study showed that differentiated thyroid cancers of follicular cell origin, especially papillary thyroid cancer, are more frequent in woman than in men (18, 19). Previous studies concluded that individuals who are working in places with possible emission of radioactive substances are more prone to develop malignant thyroid tumors (20-22). The ionized beam stimulates follicular cells to mutate genetically and intracellular cell signaling alterations are induced which can progress to malignant transformation. On the contrary, none of the MTTs patients in the current study is working in places emitting ionizing radiation. These results clarify the contribution of many risk factors (not only ionizing radiation) in the etiology of MTTs. There has been a steady rise in the frequency of thyroid cancer globally; particularly, the new cases of PTC have risen by 240% in the last three decades (23). This increase MTTs have been observed in both genders and among all races and is thought to be primarily due to an increasing trend in the rate of diagnostic imaging (24, 25).

PTC is the most common endocrine cancer and is responsible for 96% of all new endocrine malignancies, in addition, 66.8% of deaths due to endocrine cancers are caused by PTC (26). The current study showed that PTC is the most frequent type of the primary malignant thyroid carcinoma. While other types such as (FTC-minimally invasive) and HCC were reported as rare types of the differentiated thyroid cancer. A previous study revealed that medullary thyroid carcinoma account for 1-2% of MTTs while anaplastic thyroid carcinoma account for less than 1% (27), Only one case for each of MTC-minimally invasive and ATC-Spindle cell epithelioid were reported in this study.

Previous studies reported that more than 95% of all thyroid carcinoma are diagnosed as a differentiated thyroid cancer (27), that originates from thyroid follicular cells and undergone the classification of well-differentiated thyroid cancers (28). In line with our findings, Bonnefond, et al, showed that most frequent MTTs were PTC; followed by FTC, MTC, then the ATC which was very rare (29).

Bonnefond, et al, showed that 80-85% of the MTTs were PTC, which was the most common type; FTC was account for 10-15% then MTC was 3-4% and ATC 1-2%, however, it did not mention the HCC percentage (29), one possible cause may be, Bonnefond, Simon, and Terry F. Davies classify the HCC as variant of FTC. Blood group antigens are glycoproteins that expressed on the surface of red blood cells, vascular endothelial cell and neuron. The ABO blood groups are defined by carbohydrate moieties displayed on the surface of red blood cells and attached to a protein backbone, known as the H antigen (30).

We measured the prevalence of different blood groups among MTT patients, and when we did a search in medical internet engines, we found only one research (31) studied blood group distribution among MTT. In this study blood group A was the commonest type (34%) followed by blood group O, B, and AB. These results are in line with findings of Tam, Özdemir et al, who revealed that the most frequent blood group type among MTT was blood group A (44.8%).

Moreover, 90% of the MTT patients was Rh positive, which is very close to the results of Tam, Özdemir et al, who found that 91% of MTT patients are Rh positive (31). Clinical studies suggest that ABO blood groups play a role in a variety of diseases including malignancies. Gastric and pancreatic cancers are the ones with the most strong evidence of increased risk of development in certain blood groups (32). In a large prospective population-based study including more than one million donors who were followed for up to 35 years, blood group A was associated with a higher risk of gastric cancer compared to blood group O (33).

The mechanisms underlying the association between ABO blood groups and some type of tumors were not clearly explained (31). Hakomori et al, showed that the blood group antigens expressed on the surface of malignant cells were different from the antigens expressed on normal cells (34). This modified expression of blood group antigens on the surface of cancer cells may contribute to the development and progression of cancer by changing cell sensitivity to apoptosis and immune escape (35).

Another hypothesis is decreased tumor immune response due to the similar structure of certain tumor antigens with ABO antigens. One of the best known is Forssmann antigen. It is synthesized predominantly in gastric and colon tumors, and it is almost identical to the A antigen determinant structurally. This might cause inability of the immune system to recognize and attack tumor cells that express Forssmann antigen in subjects with blood group A (35). The host inflammatory response is another potential mechanism underlying the association between the ABO blood types and cancer. Inflammatory cells and mediators were reported to induce tumor development (36).

Li, Chengzhuo, et al, showed that 62% of the tumor size was bellow 2cm and 27.1% was between 2-3.9 cm and 10.9% greater or equal to 4cm. However, the current study showed that the median (IQR) of tumor size of PTC patients were 1.35 (0.8-1.9) cm, and this is similar to Li, Chengzhuo, et al study (37). Furthermore, the current study revealed that the tumor size for

MTC, HCC, and ATC were more than 5 cm. In addition, the current study showed that 62% of PTC was unifocal, HCC and FTC were also unifocal while MTC was multifocal.

Kakudo, K1, et al, revealed that 75.1 % of their study group were having spread to regional lymph nodes (38) while the current study showed LN metastasis accounts for 30.43% of the PTC patients. This may be due to early detection of MTT due to early performing FNA for suspected cases. Moreover, 29.17% of the DTC patients were documented positive lymph node and this observation was similar to results of Kakudo, K1, et al, and Li, Chengzhuo, et al, as both showed that 41.8 % of the DTC patients were positive lymph node metastasize (37, 38).

Both MTC and ATC patients in the current study were having positive lymph node metastasis. The current study showed that 97.92% of the DTC patients were in the stage I. This early detection may be due to early expectation of MTTs with suggestive clinical features like neck swelling then using diagnostic imaging techniques and microscopic examination of thyroid smears and biopsies. These findings are parallel to Li, Chengzhuo, et al, who found that 82.9% of DTC patients were in stage I and 14.5% were in stage II while the remaining patients were in stage III and stage IV (37). Furthermore, in the current study, only one PTC patient was in stage II, in addition, MTC was in the third stage and the ATC at the fourth stage (37). These data may reflect the early detection and slow growth of the DTC; thus early application of diagnostic techniques plays a critical role in the early detection of DTCs.

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