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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: the commonest type of malignant thyroid carcinoma was Papillary thyroid carcinoma (PTC) [n=46, (92%)], while all other types were uncommon, they were follicular thyroid carcinoma [(n=1) 2%], medullary thyroid carcinoma [(n=1) 2%], Hürthle 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 group is identified by existence of particular antigens on the red blood cell surfaces (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 enrolled in

this study confirmed histopathologically to have primary thyroid carcinoma and those patients who did not diagnosed as thyroid carcinoma histopathologically 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 July 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 recorded. The ABO blood groups (A/B/AB/O) and Rh factor were identified using haemagglutination method, and latest edition of American Joint on Committee on Cancer was used for Clinicopathological staging (8). Data analysis was done through (SPSS, Chicago, II, USA), version 26. Medians and Interquartile Ranges (IQR) were used for skewed variables and normal distributed data expressed through mean and standard deviation (SD) (9-12).

Results

The study showed that most of the thyroid malignant patients were females (n= 35, 70%), and males percentage was account 15 (30%); the male to female ratio was (1:2.3). Majority of patients were in 31- 50 years old age group (n=31, 62%). The frequency rate of thyroid carcinoma was more in Sulaymaniyah city (n=17, 34%) followed by Hawler (n=10, 20%), (table 4-1). The most frequent occupation was homemaker (n=29, 58%) followed by employee (n=11, 22%). 46 out of 50 patients diagnosed as papillary thyroid carcinoma that account (46%), follicular thyroid carcinoma account for (n=1, 2%), medullary thyroid carcinoma (n=1, 2%), Hürthle cell carcinoma (n=1, 2%) and undifferentiated thyroid carcinoma which is called anaplastic thyroid carcinoma account for (n=1, 2%).

Different blood group antigens were observed among patients. The blood group A with Rh positive has more frequency rate (n= 17, 34%), 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: Demographic characteristics of the study population	
Category	**Patients =*n*(%)**
Sex	
Male	15(30)
Female	35(70)
Total	50(100)
Age (Year)	
11-30	9(18)
31-50	31(62)
51-70	7(14)
71+	3(6)
Total	50(100)
Mean ± S.D	41.7±14.1
Residency	
Sulaymaniyah	17(34)
Hawler	10(20)
Other resident	23(46)
Total	50(100)
Occupation	
Homemaker	29(58)
Employee	11(22)
Other occupation	10(20)
Total	50(100)

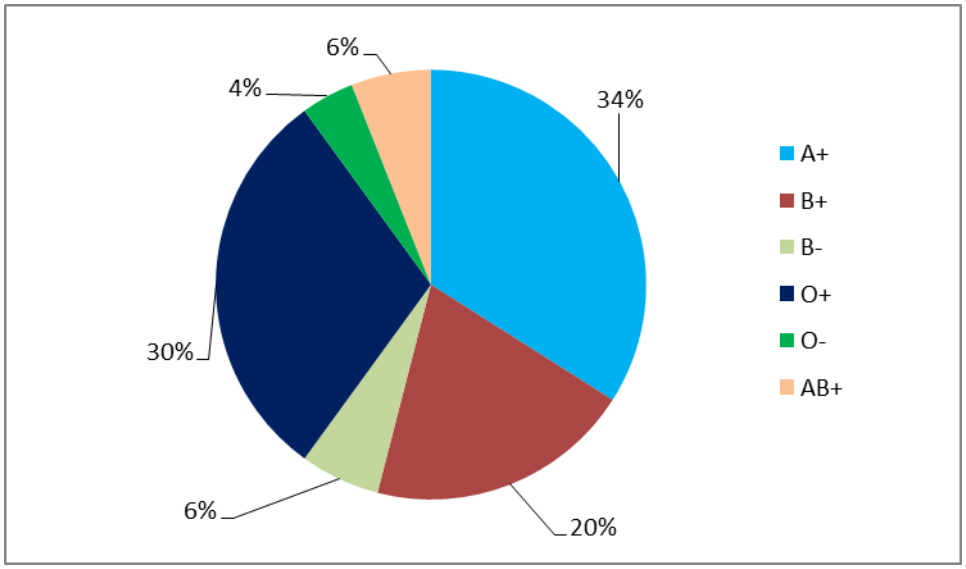

Figure 4-1: Blood Group distribution among study population.

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	Unifocal	
	n (%)	*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.			

The present study showed that 16/50 was lymph node invasion; 30.43% of patients with Papillary thyroid carcinoma had lymph node invasion, both FTC and HCC did not have metastasis while MTC and ATC cases have lymph node metastasize (table 4-4).

Table 4-4: Metastasize of Thyroid Cancers Regarding lymph node invasion		
Thyroid malignancy types	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, ATC patient was in the fourth stage IVB with pT4a N1 M0, both HCC and FTC patients were at first stage with pT3a NX MX and pT1b N0 respectively, while MTC was in third stage with pT3a N1a Mx. Among PTC group only 2.2% of PTCs were in stage II with pT3a N1a, and the remaining were in the first stage with different pathological staging as described in table (4-5).

Table 4-5: Clinicopathological staging of different thyroid carcinomas according to American Joint Committee on Cancer (AJCC).

Clinical Stage	Pathological Stage*	*n* (%)
PTC=46		
I	pT1N1b	1 (2.2)
	pT1a	11 (23.9)
	pT1aN0	6 (13.0)
	pT1aN1a	1 (2.2)
	pT1aN1b	1 (2.2)
	pT1b	8 (17.4)
	pT1bN0	4 (8.7)
	pT1bN1a	1 (2.2)
	pT1bN1b	3 (6.5)
	pT2	2 (4.3)
	pT2N0	1 (2.2)
	pT2N1b	5 (10.9)
	pT3aN1a	1 (2.2)
II	pT3aN1a	1 (2.2)
FTC=1		
I	pT1b N0	1 (100)
HCC=1		
I	pT3a NX MX	1 (100)
MTC=1		
III	pT3a N1a Mx	1 (100)
ATC=1		
IVB	pT4a N1 M0	1 (100)

*According to American Joint Committee on Cancer (AJCC) (8).

Discussion

Gender disparity in occurrence rate, disease violence, and diagnosis has been recorded in different types of malignancies. The present study showed that the frequency rate of thyroid carcinomas was 2.31 times more frequent females than in men. Jonklaas J, et al, and Rahbari R , et al. (13, 14) recorded parallel observations. Females are more prone to have thyroid diseases especially in terms of autoimmune diseases, in which stimulate pathological deviations that may participate to malignant transformation. It has been hypothesized that menstrual, environmental and reproductive factors may account for gender disparity in malignant thyroid tumor incidence rate (13, 14).

Sex hormones have an important role in developing different types of cancers and are well recognized for prostate and breast. Hormone-specific nuclear receptors (HSNR) control gene appearance and cancer cell biology are the principle mechanism of sex hormones in malignant tumor development (15). The effect of estrogen is facilitated by α- and β-estrogen receptors and these are

expressed in papillary thyroid malignancies. Furthermore, proliferating rate of thyroid cancer cells is increased by estrogen compared with male sex hormones (16, 17). Different histological subtypes in thyroid carcinomas are specific to sex disparity. The current study discovered that three histological subtypes of thyroid malignancies (Medullary thyroid carcinoma, Follicular thyroid carcinoma, and Hürthle cell carcinoma) are only present in females; on the other hand, anaplastic thyroid carcinoma was present only in male.

The present study showed that differentiated thyroid malignancies especially papillary thyroid carcinoma are more frequent in females than male, similar observations were recorded by Ortega J, et al, and Chen AY, et al, (18, 19). Previously studies showed that peoples work in places with radioactive substances have more chance to develop malignant thyroid tumors (20-22). The ionized beam excites follicular cells to transform genetically and intracellular cell signaling modifications, and the induced cells progress to malignant transformation. On the contrary, no one in MTT patients in the present study was working or living in areas with emitting ionizing radiation. These outcomes explain the contribution of many risk factors (not only ionizing radiation) in the etiology of thyroid malignancies. The frequency rate of thyroid carcinomas was rise sharply more specifically PTC cases, in which PTC increased 240% in the last three decades (23). This increment observed both sexes and among all races, and is supposed to be due to an increasing trend in the rate of diagnostic imaging (24, 25).

96% of all new diagnosed endocrine malignancies are PTC, in addition, responsible for 66.8% of deaths due to endocrine malignant tumors (26). The recent study showed that commonest type of primary thyroid carcinoma was PTC, and other histological types such as (FTC-minimally invasive) and HCC were recorded as rare types that underwent to differentiated thyroid malignancy. Medullary thyroid carcinoma account for 1-2% of thyroid malignancies and anaplastic thyroid carcinoma account for less than 1% (27), and only one case for each type of MTC and ATC were recorded in this study.

A previous study showed that above 95% of all thyroid malignancies are diagnosed as a differentiated thyroid carcinoma (27), 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, and ATC was very rare histological type (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 specific antigens displayed on the red blood cell surfaces and attached to amino acid chain backbone, known as the H antigen (30).

We measured the prevalence of different blood group antigens 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). ABO blood groups play a critical role in a variety of diseases including cancers. Gastric and pancreatic cancers are the ones with the most strong evidence of increased risk of development in certain blood groups (32). Blood group A was associated with a higher risk of gastric malignancy when compared to blood group O, this fact was observed in a large prospective population-based study including more than one million donors who were followed for up to 35 years (33).

The association mechanisms between ABO blood groups and some type of tumors were not obviously explained (31). Hakomori et al, suggested that the blood group antigen expression were different between malignant cells normal cells (34). This difference expression of blood group antigens may contribute to the development and progression of malignant cells by changing cell sensitivity to apoptosis and immune escape (35).

Another theory is declined 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 possible

mechanism that shows the association between the ABO blood types and malignant tumors. Inflammatory cells and mediators were reported to prompt 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, present 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 regional lymph node invasion (38) while the recent study showed LN metastasis accounts for 30.43% of the PTC patients. This may be due to preforming early fine needle aspiration cytology for suspected cases. Moreover, 29.17% of the DTC patients were reported with invasion of lymph node by the malignant cells and this observation was parallel to outcomes of Kakudo, K1, et al, and Li, Chengzhuo, et al. as both revealed that 41.8 % of the DTC patients were lymph node metastasize (37, 38).

Both MTC and ATC patients in the present study were having lymph node invasion. The current study showed that 97.92% of the DTC patients were in early stage (I). This early detection may be due to early expectation of MTTs with suggestive clinical features, using diagnostic imaging techniques and microscopic examination of thyroid smears and biopsies. These observations are comparable to Li, Chengzhuo, et al, who found that 82.9% of DTC patients were in early stage (I) and 14.5% were in stage II while the remaining patients were in stage III and last stage (IV) (37). Furthermore, in the present study, only one PTC patient was in stage II, in addition, MTC was in the third stage and the ATC at the last 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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