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Detection of Severity of Thyroid Cancer Using Van Kossa Stain in Iraqi Patients

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ABSTRACT

Objective: *To determine the severity of papillary thyroid cancer spread within the tissue using Van kossa stain as a tissue marker indicating the presence of calcifications within the tissue, as well as to estimate thyroglobulin and antithyroglobulin in the serum of cancer patients.* ***Method:*** *For this purpose, tissues have been taken from 50 patients samples with thyroid cancer and 30 samples from healthy individuals as a control group. fallowed by stain with Van kossa stain, for estimating the percentage of calcification within cells. The percentage of thyroglobulin and anti-thyroglobulin in the blood serum of patients was also measured.* ***Results****: The results varied; concerning age and sex, similar percentages were recorded for both genders, which were included in the study since no significant difference was found between them. As for age groups, the group with the highest recorded incidence was the age of 50 and above, where a significant difference was found between this age group and the other groups. Regarding the clinical spread of the disease, papillary thyroid cancer patients recorded a score of 3 higher than the rest, and the results showed a significant difference between them and the other groups. Regarding the presence of Psamomma bodies, smaller numbers were recorded within the tissue than in the other groups. The results of estimating thyroglobulin and anti-thyroglobulin in cancer patients showed a clear increase in both levels as compared to healthy controls.* ***Novelty:*** *The results demonstrated the role of Van kossa stain as a marker for calcifications in the tissues of the thyroid gland affected by papillary thyroid cancer, as different numbers were recorded according to the severity of the disease. We also found a significant increase in the levels of Anti Tg and Tg, which gave a close correlation with the severity of the disease and its recurrence within the human body.*

INTRODUCTION

Thyroid cancer is one of the most prevalent forms of cancer that affects the endocrine system. It is also one of the most common types of cancer. There has been a rise in the number of cases of this particular form of cancer in recent years [1],[2]. Despite the fact that it can be identified and treated at an early stage, environmental factors are increasingly responsible for its growing incidence.The increased use of chemicals in the environment, as well as exposure to heavy metals, air pollution, and radiation, are all variables that can increase the likelihood of developing thyroid cancer [3],[4]. Disorders of sleep, mental anguish, and weariness are among the most often reported symptoms of thyroid cancer. Anxiety and sadness are also among the most common symptoms. In addition to hoarseness, numbness and a palpable lump in the region of the thyroid muscle are frequently observed [5]. Histological testing, which may also detect and identify smaller tumors, is frequently used to identify the tumor [6].

Accounting for ninety percent of all occurrences of thyroid cancer, papillary thyroid cancer is the most prevalent form of the disease [7],[8]. It is the most prevalent kind of

thyroid cancer in children, accounting for roughly 90 per cent of all occurrences [9], although it is uncommon in infants and young children. Individuals between the ages of 30 and 50 [10] are often the ones that experience the highest occurrence. Tumors that are less than 1.5 centimeters in size often have a relatively favorable prognosis and are able to be easily treated surgically. Two of the aggressive subtypes of papillary thyroid carcinoma in this field are tall cell and follicular forms [11]. The lymph nodes in the neck are frequently affected by papillary thyroid carcinoma, which is a kind of thyroid cancer that affects roughly 70 percent of patients [12].

In the thyroid, papillary carcinomas account for more than 90 per cent of all tumours. Thyroglobulin is the most essential diagnostic marker for these tumours since it is a vital component in the production of thyroid hormones [13] and is produced by differentiated thyroid cells [14]. This makes it the most important for determining whether or not these tumours are present. The thyroid gland's follicular epithelial cells are responsible for the production of this protein, which has a molecular weight of 330 kDa and is made up of 2750 amino acids [15].

Van Kossa Stain is a method used to identify mineral deposits in tissues, specifically calcium and phosphate [16]. The name of the dye comes from the scholar who was responsible for its discovery. Horses and rabbits were used in the initial trials for the dye, which concentrated on inducing kidney calcification in animals by providing them with a variety of poisons, with the primary emphasis shifting to biological reactions and the quantitative analysis of organic substances [17]. Scientists in the nineteenth century used silver salts to stain skin and internal organs with a dark grey color [18].

RESEARCH METHOD

Figure 1 summarize the main methods and the outcome of the study. Starting with collecting samples and ending with the diagnosis using Van Kosa stain and estimate thyroglobulin and anti-thyroglobulin in the serum of cancer patients .

Samples collection

The samples were collected from Ghazi Hariri Teaching Hospital/City Hospital in Baghdad from patients diagnosed with thyroid cancer. The study included 50 samples from patients with thyroid cancer and 30 samples from healthy individuals as a control group. Histological sections embedded in paraffin blocks, previously diagnosed as thyroid cancer, were used in the study after being reviewed by a pathologist, taking into account the patient's age and sex . 6 ml of blood were collected from both the patients and the healthy individuals. The blood was then separated, and the serum was used for the tests included in the study.

The study design has been approved by the College of Science Research Ethics Committee in University of Baghdad (Ref. No.0923/0074, dated to the 25th of September 2023).

Von Kossa staining method

The paraffin was removed using xylene. The samples were then hydrated with distilled water and immersed in a solution. The slides were placed in a prepared 5% silver

solution and left in sunlight for one hour. The slides were then washed with distilled water, placed in the stain for 5 minutes, washed again with water, and allowed to dry. Finally, a coverslip was placed over the slide.

Thyroglobulin (Tg) and anti-thyroglobulin (anti-TG)

The levels of Tg and anti-Tg were measured in serum using the Roche Cobas e411 automated analyzer, which employs electrochemiluminescence immunoassay (ECLIA) technology. The assay time was 18 minutes. The TG and anti-TG assays used biotinylated monoclonal antibodies labelled with ruthenium. Roche provided the calibrators, reagents, and quality control materials.

Statistical analysis

The Statistical Packages of Social Sciences -SPSS (2019) program was used to detect the effect of difference groups (Type of cancer) in our study parameters. T-test and Least significant difference-LSD was used to significant compare between means. Chi-square test was used to significant compare between percentage (0.05 and 0.01 probability) in this study.

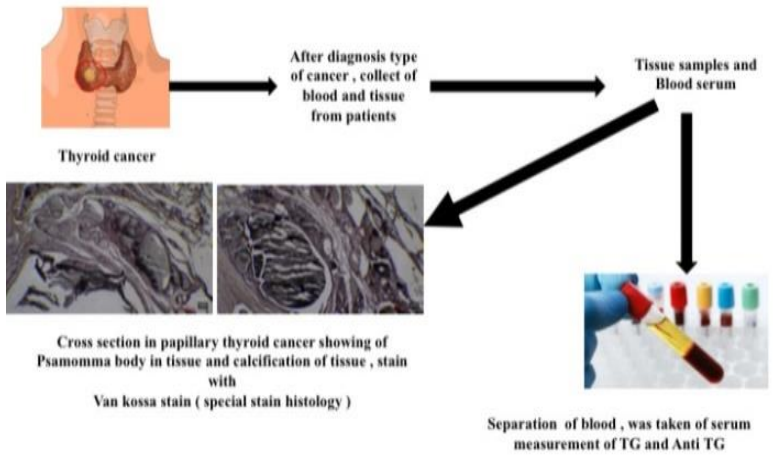

Figure 1. Summary illustrate the main practical steps and the findings of the research.

RESULTS AND DISCUSSION

The results, as shown in statistical table 1, regarding sex, indicated that the incidence of papillary thyroid cancer was higher in males (57.78%) than in females (42.22%). Similarly, in the control group, the percentage of males was higher than that of females (56.67% vs. 43.33%), but this difference was not statistically significant (p-value = 0.2166). The age groups were divided into three categories. The mean value for papillary thyroid cancer (48.37±1.48) was recorded for each of the three age groups, while the mean value for the control group (41.67±2.63) was also recorded. A statistically significant difference was found between the two groups (P=0.0178*) (table no.1).

Table 1. Relationship between Type of Cancer with Gender and Age in sample study.

Factors		Papillary carcinoma No (%)	Fibrosis No (%)	Normal No (%)	P-value
Gender	Male	26 (57.78%)	3 (60.00%)	17 (56.67%)	0.2166 NS
	Female	19 (42.22%)	2 (40.00%)	13 (43.33%)	
Age (year)	<40 yr.	9 (20.00%)	3 (60.00%)	15 (73.33%)	0.0294 *
	40-50 yr.	17 (37.78%)	2 (40.00%)	7 (0.00%)	
	>50 yr.	19 (42.22%)	0 (0.00%)	8 (26.67%)	
	Mean ±SE	48.37 ±1.48 a	37.00 ±2.77 b	41.67 ±2.63 ab	0.0178 *
Total		45	5	30	---

* (P≤0.05).

In papillary thyroid cancer, the severity of calcification was recorded as zero (8.89%), while the severity was recorded as high (20%), medium severity was recorded as 17.78%, and low severity was 53.33%. As for the fibrosis group, 40% recorded zero severity and 20% high severity, while the percentage of medium was zero, and low severity was 40%, where there was a highly significant difference Table (2).

The results that show the relationship between the type of cancer and the score are as follows: For papillary thyroid cancer, score (0) recorded a percentage of 28.89%, while score (1) recorded a percentage of 24.44%, score (2) recorded 26.67%, and score (3) recorded 20%. In the fibrotic group, score (0) and score (1) both recorded 40%, while score (2) recorded 20% and score (3) recorded 0%. There was a significant difference between the two groups, as shown in Table (3) and Figure (2).

Table 2. Relationship between Type of Cancer and Found calls in sample study.

Variable		Papillary carcinoma No (%)	Fibrosis No (%)	P-value
Found Calcification	No	4 (8.89%)	2 (40.00%)	0.0007 **
	High	9 (20.00%)	1 (20.00%)	
	Moderate	8 (17.78%)	0 (0.00%)	
	Low	24 (53.33%)	2 (40.00%)	
Total		45	5	---

** (P≤0.01).

Table 3. Relationship between Type of Cancer and Score in sample study.

Variable		Papillary carcinoma No (%)	Fibrosis No (%)	P-value
Score	0	13 (28.89%)	2 (40.00%)	0.0496 *
	1	11 (24.44%)	2 (40.00%)	
	2	12 (26.67%)	1 (20.00%)	

	3	9 (20.00%)	0 (0.00%)	
Total		45	5	---

* (P≤0.05).

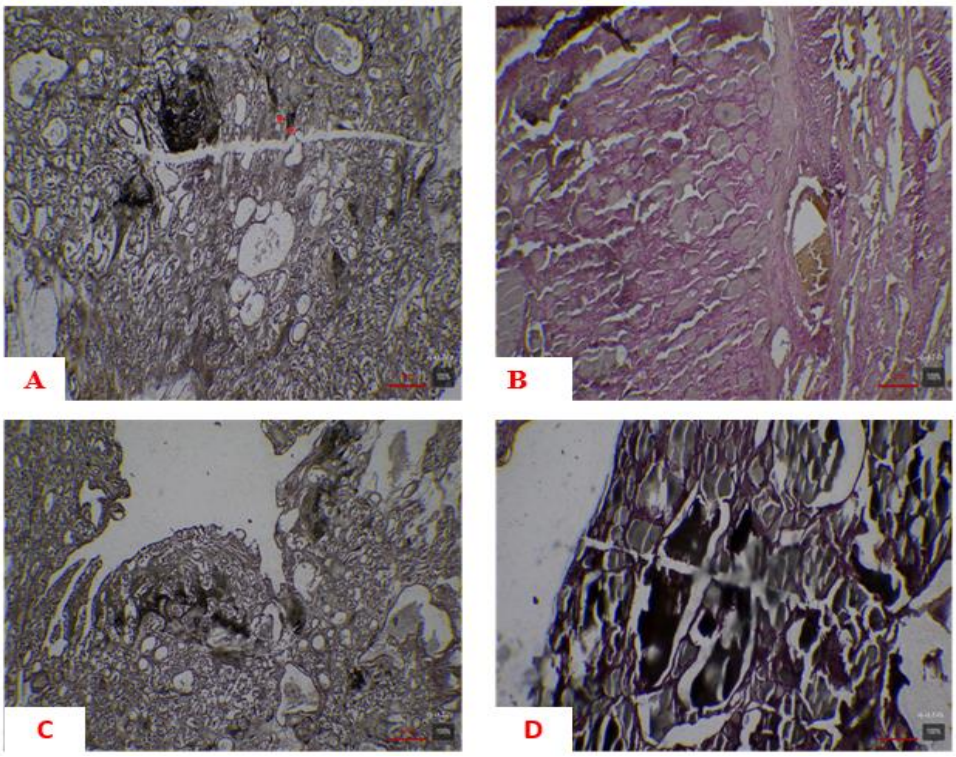

Figure 2. Cross section in Thyroid gland infected with papillary thyroid cancer stain with Van kossa stain , A: negative staining score 0 , no black discoloration seen, 10X, B: positive staining score (1) showing blacking color seen in section , 10X, C : positive staining score (2) showing blacking color seen in section , 10X, D: positive staining score (3) showing blacking color seen in section , 10X.

The results indicated varying percentages of toxin particles in papillary thyroid cancer, with an arithmetic mean of (3.80 ± 0.56) for the papillary thyroid cancer group and (0.40 ± 0.20) for the fibroid group, revealing a highly significant difference between the two groups. Table 4, Figure (3).

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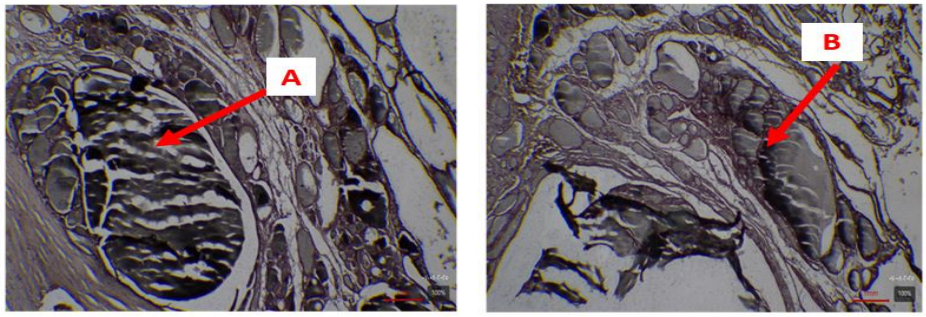

Figure 3. Cross section in thyroid gland stain with Van Kossa stain , 40X , showing of (A: Psammoma bodies is large shape appearance in collided of gland infected with Papillary thyroid cancer , B: Psammoma bodies (calcification) in tissue is smaller than in (A) , 40X.

Table 4. Relationship between Type of Cancer and Psammoma bodies in slide in sample study.

Variable		Papillary carcinoma No (%)	Fibrosis No (%)	P-value
Psammoma bodies in slide	0	11 (24.44%)	4 (80.00%)	0.0046 **
	1-5	21 (46.67%)	1 (20.00%)	
	6-10	9 (20.00%)	0 (0.00%)	
	>10	4 (8.89%)	0 (0.00%)	
	Mean ±SE	3.80 ±0.56 a	0.40 ±0.20	0.0001 **
Total		45	5	---

* (P≤0.05), ** (P≤0.01).

Table 5. Relationship between type of cancer with Tg and Anti-Ag.

Type of Cancer	Mean ±SE	
	Tg	Anti - Ag
Papillary carcinoma	0.631 ±0.12 b	1.103 ±0.18 a
Fibrosis	0.325 ±0.17 b	0.536 ±0.38 ab
Normal	24.80 ±1.39 a	0.245 ±0.05 b
L.S.D.	3.876 **	0.811 **
P-value	0.0001	0.0017

Means having with the different letters in same column differed significantly. ** (P≤0.01).

There is a relationship between gender and age in human papillary thyroid cancer. The incidence of thyroid cancer varies between the sexes. Studies have indicated that the incidence in females is three times that of males, especially in papillary thyroid cancer. This is what has been proven [19]. Some studies have identified male gender as a factor positively associated with poor outcomes in patients treated surgically [20]. Other researchers and studies have concluded differently, as indicated by references [21],[22]. However, in our study, the groups varied, with males recording higher incidence rates than females. The finding provides an important explanation, as gender is not considered

an important factor in determining patients, and this is the correct opinion, given the disparity in studies between the sexes. Large population studies have shown that men have a significantly lower incidence of papillary thyroid cancer than women. Several studies have reported that gender was not a predictor of papillary cancer [23],[24].

This difference drives the adoption of healthcare systems between countries. Previous studies have shown that individuals aged 25-34 and 35-39 years tend to have the highest incidence of this type of cancer, and this rate was recorded in Canada compared to the United States [25]. This information is consistent with the results of the experiment, as this age group recorded a higher rate than other groups. Liu et al. (2007) provide evidence that age groups play a significant influence in determining the prevalence of thyroid cancer. A higher exposure to radiation during childhood and adolescence is the reason for the high incidence of thyroid cancer among young age groups in Canada. This reason is closer to explaining the results than any other reason. Continuous exposure to radiation over extended periods of time (during infancy and adolescence) or over diagnosis are the factors that contribute to the spread of papillary thyroid cancer, as our study included these age groups as participants. An increase in the presence of calcification was found to be associated with heart and vascular diseases in two groups of patients who had calcification, according to studies that were conducted on the subject [26]. Calcification and cancer have been linked in a number of studies, which provide evidence that this connection exists. As one of the characteristics of papillary polymorphic thyroid cancer, fibroma bodies might be a source of diagnostic difficulties.

Since this study is quite similar to the findings of the research that was carried out [27], Labay et al. discovered that fibroma bodies were present in 58 out of 229 cases of patients who had papillary thyroid cancer. This correlation was statistically significant. In comparison to a group of benign lesions, BB bodies and calcifications were observed in a study that was carried out by Konorty and colleagues [28].it was found that psammoma bodies occupy cells that have been affected by infarction and necrosis of papillary cancerous structures. The calcified aggregates that make up psammoma bodies are spherical in shape and range in diameter from fifty to seventy micrometres [29]. Several research studies have been carried out regarding the connection between psammoma bodies and benign tumours. These investigations have found that the percentage of psammoma bodies that are benign is modest and varies, as was the case in the study that Hunt et al. [30] undertook. Given that the existence of these structures in benign tumours was extremely uncommon , it has now come to light that there is a significant connection between these bodies and papillary thyroid cancer. A different study found that the majority of cases of adenoma that are accompanied by psammoma bodies are of the tumour type. These studies are approximate representations of the outcomes that were seen in the experiment. Another reason is the infarction of tumours or a defect in the creation of blood vessels [31], and agree with this explanation because it offered clear evidence concerning the genesis of these bodies. As a result, we believe that this explanation is correct. Studies have shown that samples of papillary thyroid

cancer stained with Van Kossa yielded a positive result, as 100% of malignant thyroid samples tested positive, including 15 specific samples [32].

Other studies have investigated the role of Van Kossa stain, proving that this stain interacts with phosphate, not calcium. It is possible to observe that the phosphate group is associated with tissue malignancy [33] [34]. This stain has recently been used in the diagnosis of papillary thyroid cancer [35]. In some studies, 232 patients tested positive for this strain [36]. It confirms the existence of a relationship between Van Kossa stain and the characteristics of aggressive papillary thyroid cancer, as it was found that the positive stain occupies an independent indicator of central lymph node metastases.

Therefore, the positive Van Kossa stain in thyroid cancers may be a useful indicator of lymph node metastases.Previous studies have shown that patients with progressively rising levels of TG antibody have a significantly increased risk of approximately 40%, while those with stable levels are either disease-free or healthy [37]. A study by Latrova et al. showed that the patterns of TG antibody vary greatly. They showed that antibodies associated with papillary thyroid cancer arise from an antitumor immune response, which may be due to a change in the antigen or post-translational modifications of thyroglobulin in malignant tissues [38]. This study agreed with our results, as it showed an increase in TG antibody in papillary thyroid cancer patients. As Dorita et al. [39] demonstrated in Graves' disease and subacute thyroiditis, serum TG consists of high-molecular-weight forms, reflecting its release from normal thyroid cells during the synthesis of stimulating hormones, while in papillary thyroid cancer patients, TG with a low molecular weight appears. Lower molecular weight with distinct immunophenotypes indicating altered processing by malignant cells. Some studies have shown no significant association between serum Tg-Ab levels and disease progression, while other studies have shown that persistent Tg antigen indicates disease recurrence [38]. it is a very positive prognostic indicator for this type of cancer, especially for those who have undergone total thyroidectomy.

CONCLUSION

Fundamental Finding : The results demonstrated the role of Van kossa stain as a marker for calcifications in the tissues of the thyroid gland affected by papillary thyroid cancer, as different numbers were recorded according to the severity of the disease. We also found a significant increase in the levels of Anti Tg and Tg , which gave a close correlation with the severity of the disease and its recurrence within the human body. **Implication:** We also found a significant increase in the levels of Anti Tg and Tg , which gave a close correlation with the severity of the disease and its recurrence within the human body. **Limitation :** This study was limited by the scope of sample collection, which was restricted to a single institutional setting, potentially affecting the generalizability of the findings. In addition, the analysis focused primarily on histopathological staining and selected biochemical markers, without incorporating molecular or genetic assessments that could provide deeper insight into disease progression. **Future Research :** Future studies are recommended to involve larger,

multicenter populations to validate the diagnostic and prognostic value of Van Kossa staining across diverse clinical settings. Further research integrating molecular, genetic, and longitudinal analyses is also needed to better elucidate the relationship between calcification patterns, biomarker levels, disease severity, and recurrence in papillary thyroid cancer.

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