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RESEARCH ARTICLE

USE OF DIAGNOSTIC TESTS FOR DETECTION OF MALIGNANT THYROID NODE AND ITS CONCORDANCE WITH THE CITOPATOLOGICAL CHARACTERISTICS IN PATIENTS OF THE HIGH SPECIALTY NAVAL GENERAL HOSPITAL

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ABSTRACT

Introduction: Thyroid cancer is considered the most frequent endocrine neoplasm, the American Association for the Study of the Thyroid (ATA), projected that by 2019 it becomes the third non-fatal cancer in the order of prevalence in women. The thyroid nodule as its most frequent form of presentation, through the use of ultrasound with high spatial resolution, can be captured in 19-67% of healthy individuals. Among the large number of thyroid nodules detected, only 5% -15% are only 5% to 7% of cases. For the differential diagnosis of these thyroid nodules, fine needle aspiration (FNAB) is considered an accurate and cost-effective method for evaluation with a high sensitivity and diagnostic specificity; Associated with this, it has been considered that the elevation of some scabies markers indirectly malignant nodular degeneration. Few studies have evaluated the statistical power in the achievement of ultrasonographic parameters as biochemical in the prediction of the malignant thyroid nodule, which would co-contribute in the clinical act. **Objetives:** To establish the diagnostic correlation between the serum levels of Thyrotropin and Anti-Tritoglobulin Antibodies and the ultrasound findings that allow the prediction of malignant thyroid nodule development using the BETHESDA and TI-RADS classifications. **Material and Method:** An observational, cross-sectional, comparative and ambispective study was carried out. Temporary-spatial location of the study: April 2016 to March 2018, Radiology service of the Naval General Hospital of High Specialty. The normal distribution of the TSH values, anti-thyroglobulin antibodies (Anti Anti Tg) and patient age according to the Z value of the Kolmogorov-Smirnov statistic was studied. We use measures of central tendency using the statistical package SPSS version 21.0. **Results:** Were analyzed 136 cases associated with thyroid nodule, of which 122 (89.7%) were female and 14 (10.3%) male. Age was in the range of 19 to 77 years with an average of 48.7 +/- 14.6 years of standard deviation. Active military were 50.7% of the cases and right holders or military retired 49.3%.According to the histopathological study, 22 cases of thyroid cancer were identified for a prevalence of 16.2% in the sample of clinical suspicion; 63.2% of the cases resulted malignant neoplasia (atypia with undetermined significance, follicular neoplasm and probable thyroid cancer) and only 20.6% were benign.More than half of the thyroid nodules studied were hypoechoic (59.6%), 66.9% had vascularity, 67.9% microcalcifications, 74.3% poorly defined borders, and 48.5% wider than high positive. In 44.9% the location of the nodule was in the isthmus, 45.6% the size ranged between 1 and 2 cm, slightly more than half (52.9%) had TSH> 1.64 mU / L while 65.4% had anti-thyroglobulin antibodies> 40 IU / ml.Comparing malignant versus benign cases according to the gold standard (Bethesda scale) a TSH value> 1.64 mU / L presented 14.7 times [IC95% 4.1-51.9, p = 0.0001] plus risk of malignancy; while those above 0.40 IU / ml of anti-thyroglobulin antibodies have a 1.8-fold increased risk [IC95% 0.8-4.3, p = 0.13] of malignancy.Each Bethesda diagnosis corresponded to an ascending ultrasound score from 1.14 for non-diagnostic sample to 1.81 for probable CA and 1.95 for CA and, at the same time, it is evident that TSH levels increased correlatively and this is because the ultrasound score it is correlative (rho 0.465, p = 0.0001) to the levels of thyrotropin **Conclusion:** It is concluded that the combination of serum thyrotropin levels with an ultrasound characterization under the TI-RADS system, in right-holders of the Naval Hospital, were highly predictive of nodular malignant thyroid disease, conditioning a feasible diagnostic method for the evaluation of patients carrying thyroid nodule, thus avoiding, getting to perform unnecessary biopsies and surgeries.

INTRODUCTION

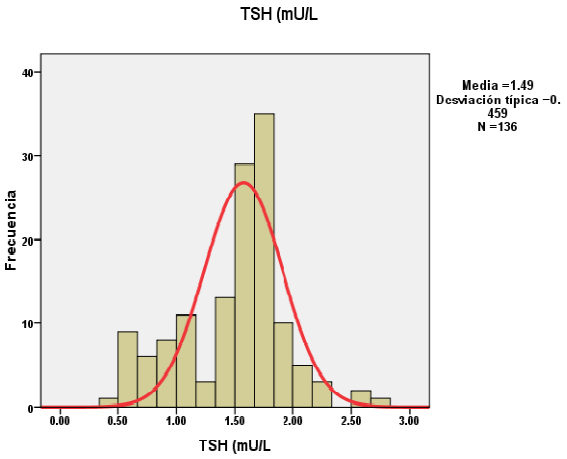
The use of Puncture by Fine Needle Aspiration is considered the reference method for the evaluation of thyroid nodules, the results are inaccurate in approximately 30% of cases. Several studies have attempted to predict the risk of malignancy in thyroid nodules based on age, nodularity, thyrotropin / TSH values, autoimmune thyroid disease, and ultrasonographic parameters. However, there is no consensus and none of these parameters has been handled together to assess the statistical power in the approach of these patients. The evaluation of indeterminate thyroid nodules and biopsies of nodules with initially benign cytological results, remain as important and controversial topics of discussion. It has been observed that levels above the normal limit of thyrotropin and anti-thyroglobulin antibodies have been strongly associated with a higher risk of malignancy for the general population. Since it would be relatively accessible to indicate to all patients with thyroid nodule an aspiration biopsy for its characterization due to its speed and diagnostic efficiency; first it would be important to understand and recognize the biochemical characteristics and the ultrasonographic appearance of the nodules to differentiate those that really merit cytological evaluation from those that do not, through homogenized criteria, handled by the competent specialists to the area. In this way, the implementation of invasive diagnostic methods, surgical treatments and unnecessary expenses would be avoided; or on the contrary, the delay of timely diagnoses.

Background

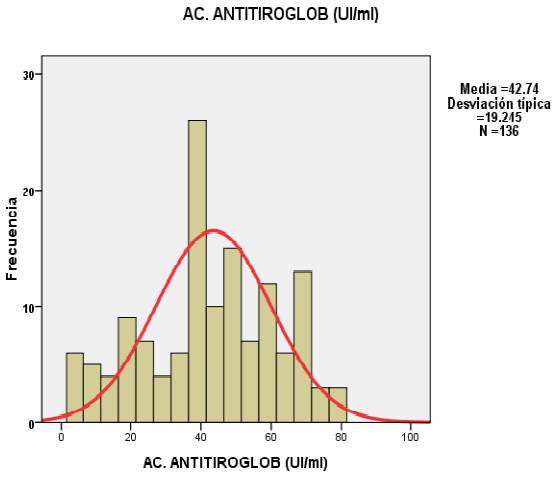
The thyroid is a frequent site of benign and malignant nodular lesions due to its rich blood supply and high metabolic activity. Epidemiological studies show a prevalence of nodular thyroid disease in 51% of the general population, 8 to 64% of autopsies and 19-35% of the ultrasounds performed by non-thyroid pathologies (incidentalomas). Despite the relatively high prevalence of thyroid nodules, thyroid cancer is relatively rare, and less than 7% of the nodules are malignant. In spite of the above, the National Institute of Health of the United States has reported an accelerated growth in the incidence of thyroid carcinoma, which was 3.8 cases per 100,000 population in 1975 and 11.9 per 100,000 population in 2010, probably explained by the earliest detection with the increase in the use of ultrasound in the detection of subcentimeter nodules, implying demographic changes, especially in the committed age groups. Most scientific endocrinology societies follow the guidelines included in the Guidelines of the American Association of Thyroid (ATA) in 2015, in which they recommend the ultrasound evaluation as part of the initial study of all the nodular lesions in the thyroid. The challenge, from the clinical and imaging point of view, is to differentiate the few malignant nodules, among the vast majority of benign ones and, therefore, to differentiate the patients in whom the surgery is indicated.

Malignancy Risk Factors

When a thyroid nodule is discovered, a complete clinical history and clinical examination should be prepared. Some risk factors for malignancy include a childhood history of radiation exposure to the chest or neck, a family history of thyroid carcinoma, Cowden's syndrome, Carney's complex, Multiple Endocrine Neoplasm (MEN), and Werner's syndrome. There is controversy if diffuse thyroid diseases such as Hashimoto's



Graph 1. Distribution of TSH values



Graph 2. Distribution of Ac values. Antithyoglobulins

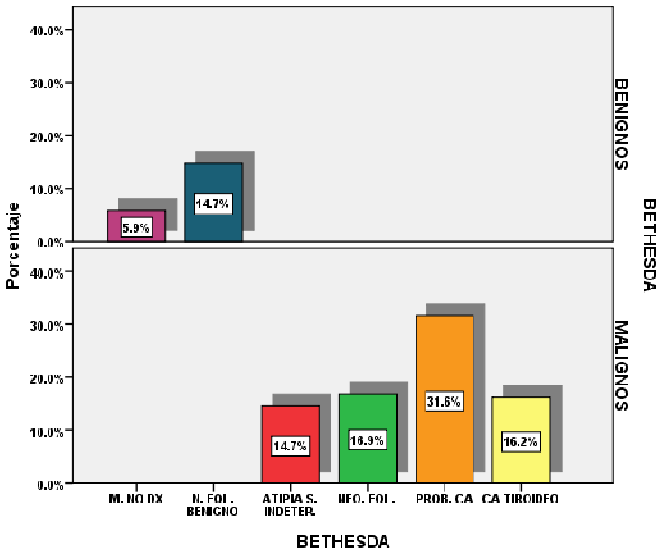


Figure 3. Distribution of cases with thyroid nodules according to the histopathological result on the Bethesda scale

Thyroiditis and Graves' Disease predispose to thyroid carcinoma. There is a clear predilection for thyroid nodules and thyroid carcinoma in women in relation to men of 4: 1 and 3: 1, respectively. Kim et al, evaluated the incidentally found thyroid nodules (incidentalomas) and found a significantly higher incidence in 58% women, compared with 28.2% of men. In general, the probability of malignancy in a thyroid nodule is greater in patients younger than 15 years and older than, and mortality increases when the patient is older than 45 years. From the pathological point of view, thyroid nodules are classified into 5 types: hyperplastic, neoplastic, colloid, cystic and indeterminate. Among the neoplastic nodular lesions we found papillary (70-80%), follicular (10-20%), anaplastic (1-2%) and medullary carcinomas (5-10%). Papillary carcinoma is the most common, corresponding to approximately 75-80% of malignant thyroid neoplasms. Papillary carcinoma is multifocal in approximately 20% of cases, being more frequent in women and is also the neoplasm that is most frequently found in children. It usually occurs before the age of 40, with frequent metastatic involvement of the cervical lymph nodes. Of the thyroid carcinomas, it has the best prognosis with a survival at 20 years of 95%. Follicular carcinoma frequently affects women in the sixth decade of life and may present with metastatic lesions to bone, brain and lungs.

Serum levels of TSH

Previous studies have shown that increased serum TSH levels may be associated with an increased risk of thyroid cancer. Boelaert *et al.* studied 1,500 consecutive patients without thyroid dysfunction and found an increased risk of malignancy (an adjusted odds ratio (OR) of 2.72) in subjects whose TSH levels ranged from 1.0 to 1.7 mU / L than in those with TSH <0.4 mU / L (OR of 1.00), with a particularly high incidence of thyroid cancer, mainly papillary. Fiore *et al.* studied the relationship between serum levels of TSH and papillary thyroid carcinoma (PTC) in patients with uni or multinodular goiter who were treated with levothyroxine. The treated patients had lower serum TSH levels and decreased PTC prevalence. The PTC prevalence was lower in patients with TSH levels <0.4 mU / ml and was higher in those with TSH levels> 3.4 mU / ml (1.9% vs. 16.5%), without influence of age or multiple nodularity. It has been proposed that TSH could cause tumor growth through the TSH receptor in well-differentiated thyroid carcinoma as in normal thyroid tissue, which results in hidden progression of the cancer. Recently, some reports presented serum thyrotropin (TSH) as a possible reliable predictor of thyroid malignancy and that it could be a risk factor for thyroid cancer since it is the most common cause of elevated TSH. TSH, could help predict malignancy in subjects with thyroid nodules. In thyroid neoplasia, the prevalence of TgAb, 10-30%, is much higher than that of the normal population and subsequently decreases after cancer treatment in 3 years. Therefore, some studies suggest that persistent increases in TgAb titers could be an early marker relapse as a substitute for thyroglobulin. These findings imply that the elevation of TgAb is present before surgery in malignant nodules. In humans, thyroglobulin has only four to six epitopes that are recognized by B cells among the 40 known epitopes. Recently, thyroglobulin produced by thyroid cancer. Therefore, it is possible for occult thyroid cancer to develop in the normal thyroid, stimulating chronic immune responses and producing new or more TgAb against thyroglobulin released by increasing tumor cells in proportion to TSH levels. This could explain the mechanism of association between positive TgAb and malignancy.

Objectives of the study

To establish the diagnostic correlation between the serum levels of Thyrotropin and Anti-Tritoglobulin Antibodies and the ultrasound findings that allow the prediction of malignant thyroid nodule development using the BETHESDA and TI-RADS classifications. Additionally, as specific objectives, it was proposed: Describe the sociodemographic characteristics of the patients under study (age, gender, affiliation) as well as the morphological characteristics of the detected thyroid nodules (location, size). Evaluate the ultrasound findings under the TI-RADS criteria, as well as its sensitivity and specificity for detection of thyroid nodule suspected of malignancy in right-holders of Naval General Hospital of high specility (HOSGENAES). Establish serum cohort points for thyrotropin and thyroglobulin antibodies as predictive values of malignant thyroid nodule in right-holders of HOSGENAES.Evaluate the ultrasound and biochemical paper to determine the need to perform a needle biopsy by aspiration with a fine needle before a thyroid nodule suspected of malignancy.

MATERIALS AND METHODS

An observational, cross-sectional, comparative and ambispective study was carried out. Temporary-spatial location of the study: April 2016 to March 2018, Radiology service of the Naval General Hospital of High Specialty. Procedure consisted in that the patient will be referred to the Endocrinology service (external consultation), taking as criteria the palpation or suspicion of thyroid nodule, where the patient will be sent to the Radiology service to assess the characteristics of the detected nodule for the first time, requesting all patients thyroid function tests as a complement.The thyroid ultrasound will be characterized by the TIRADS system in the Radiology service.If the patient is a candidate for Fine Needle Aspiration Puncture, the informed consent will be given to authorize their participation in the research study.The sample of the biopsy will be sent to the Pathology service for its staging under the BETHESDA system.The database of all patients included in the research project will be made for the subsequent contrast of the variables proposed, those patients who were included in the retrospective phase were captured according to the inclusion criteria via electronic file. The normal distribution of the TSH values, anti-thyroglobulin antibodies (Anti Anti Tg) and patient age according to the Z value of the Kolmogorov-Smirnov statistic was studied. Central tendency measures were used using the statistical package SPSS version 21.0. The linear correlation of the values of thyrotropin and anti-thyroglobulin antibodies was analyzed by the Spearman correlation coefficient (rho). To refine the relationship between the TI-RADS classification and that of Bethesda with respect to TSH levels, the general variance analysis model of two or more factors was applied.

RESULTS

We analyzed 136 cases associated with thyroid nodule, of which 122 (89.7%) were female and 14 (10.3%) male. Age was in the range of 19 to 77 years with an average of 48.7 +/- 14.6 years of standard deviation. Active military were 50.7% of the cases and right holders or military retired 49.3%.

Patients' age (Z = 0.76m, p = 0.59) and anti-thyroglobulin antibody values (Z = 1.0, p = 0.25) had a normal distribution according to the Z value of the Kolmogorov-Smirnov statistic; but the values of TSH had a Z = 2.4 (p = 0.0001) evidencing lack of normality in the distribution. TSH had an average of 1.49 +/- 0.4 (range 0-3) mU / L and anti-thyroglobulin antibodies 42.7 +/- 19.2 (range 4-80) IU / ml (Graphs 1 and 2).

Table 1. Comparison of TSH means (mU / L) between cases classified by TI-RADS as malignant and benign according to the histopathological diagnoses of the Bethesda scale

Bethesda	TI-RADS		p	Global averages
	Malignant	Benign		
Non-diagnostic sample	-	0.91 (0.13)	-	0.91 (0.13)
Benign follicular nodules	1.46 (0.18)	1.05 (0.09)	0.04	1.26 (0.10)
Benign follicular nodules	1.38 (0.12)	1.32 (0.11)	0.74	1.35 (0.08)
Follicular neoplasms	1.56 (0.09)	1.25 (0.13)	0.05	1.40 (0.08)
Probable thyroid cancer	1.79 (0.06)	1.33 (0.16)	0.009	1.56 (0.08)
Thyroid cancer	1.67 (0.07)	-	.	1.67 (0.07)
p	0.01	0.07		0.0001

Tabla 2. Comparison of anti-thyroglobulin antibody means (IU / ml) among cases classified by TI-RADS as malignant and benign according to the histopathological diagnoses of the Bethesda scale

Bethesda	TI-RADS		p	Medias globales
	Malignos	Benignos		
Non-diagnostic sample	-	38.8 (6,7)	-	38.8 (6.7)
Nódulos foliculares benignos	30.7 (9.5)	39.2 (4.7)	0.42	35.0 (5.3)
Benign follicular nodules	40.5 (6.3)	39.3 (5.7)	0.89	39.9 (4.3)
Follicular neoplasms	38.8 (4.9)	55.7 (6.7)	0.04	47.2 (4.1)
Probable thyroid cancer	41.9 (3.1)	47.0 (8.5)	0.58	44.4 (4.5)
Thyroid cancer	49.7 (4.0)	-	.	49.7 (4.0)
p	0.26	0.27		0.24

Table 3. Reasons for the probability of malignancy of thyroid nodules according to the gold standard (Bethesda) according to the TSH cut-off points

Cut points of TSH (mU/L)	Malign (n = 108)	Benign (n = 28)	Reason for the probability of malignancy	Áreas
0.38-0.62	1 (0.9%)	5 (17.9%)	0.05	
0.63-0.87	5 (4.6%)	5 (17.95)	0.25	
0.88-1.12	10 (9.3%)	7 (25.0%)	0.37	1.62 <Low diagnostic probability of malignancy
1.13-1.37	12 (11.1%)	2 (7.1%)	1.56	
1.38-1.62	6 (5.6%)	5 (17.9%)	0.31	
1.63-1.87	55 (50.9%)	3 (10.7%)	4.75	1.63 ≥Discriminating
1.88-2.12	13 (12.0%)	1 (3.6%)	3.33	
2.13-2.37	3 (2.8%)	0	-	2.13 >Confirmation of malignancy
2.38-2.62	2 (1.9%)	0	-	
2.63-2.80	1 (0.9%)	0	-	

According to the histopathological study, 22 cases of thyroid cancer were identified for a prevalence of 16.2% in the sample of clinical suspicion; 63.2% of the cases were malignant neoplasms (atypia with undetermined significance, follicular neoplasia and probable thyroid CA) and only 20.6% were benign (Graph 3) which indicates that in general terms the prevalence of malignancy amounted to 79.4%.

Note (Table 1, Graph 4) that systematically the mean values of TSH are lower in the stratum considered benign by TI-RADS although this procedure included three groups of malignant cases (false negatives corresponding to: atypia of undetermined significance, follicular neoplasia and probable thyroid cancer) identified as malignant by the gold standard (Bethesda), but correctly TI-RADS also did not include cases of thyroid cancer as if they were benign; On the other hand, evidently the TI-RADS malignant stratum did not include any case of non-diagnostic samples. Note that except in the cases of atypias of undetermined significance (p = 0.74) in all the others the TSH means between malignant and benign are significantly different with higher means for the malignant cases; Moreover, within the cases classified by TI-RADS as benign, the TSH means do not reach to be different (p = 0.07) but within those classified as malignant if they are (p = 0.01) although the follicular nodules have a higher mean (1.46 mU / L) than atypia (1.38 mU / L) and probable cancer cases also have a higher mean (1.79 mU / L) than cancer cases as such (1.67 mU / L), In any case, the tendency of TSH is to increase as one goes from a histological diagnosis to one of greater malignancy. The values of TSH and anti-thyroglobulin antibodies did not correlate linearly (rho 0.06, p = 0.46) and neither correlated with age; nevertheless, see (table 2, graph 5) that the means of anti-thyroglobulin antibodies differ significantly in follicular neoplasms in which the cases are benign by TI-RADS have a very high mean (55.7 IU / ml) compared with the colors as malignant (38.8 IU / ml); however, it is evident that this marker is not very sensitive to differentiate including the diagnostic cases by Bethesda (p = 0.24 globally) and it does not differentiate between malignant (p = 0.26) nor between benign (p = 0, 27). According to the TI-RADS study, the cases were classified as 88 (64.7%) malignant and 48 (35.3%) benign, for a sensitivity of 77.8% of TI-RADS, with respect to the histopathological analysis, specificity of 85.7%, accuracy 79.4%, positive prognostic value of 95.4% and negative of 50.0%, see (table 3) the differences by tender. More than half of the thyroid nodules studied were hypoechoic (59.6%), 66.9% had vascularity,

67.9% microcalcifications, 74.3% poorly defined borders, and 48.5% wider than high positive. In 44.9% the location of the nodule was in the isthmus, 45.6% the size ranged between 1 and 2 cm, slightly more than half (52.9%) had TSH> 1.64 mU / L while 65.4% had anti-thyroglobulin antibodies> 40 IU / ml. Comparing malignant versus benign cases according to the gold standard (Bethesda scale) a TSH value> 1.64 mU / L has 14.7 [95% CI 4.1-51.9, p = 0.0001] plus risk of malignancy;

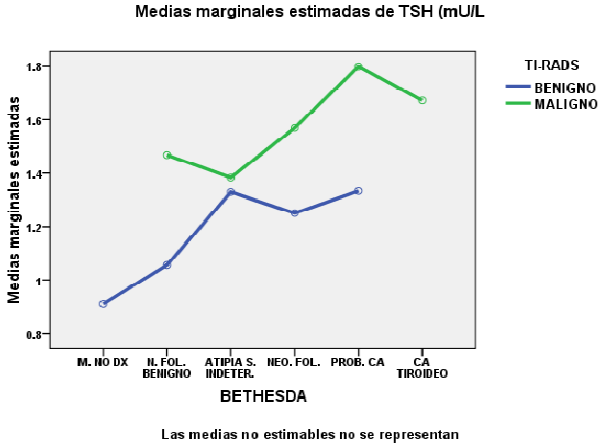


Figure 4. Comparison of TSH means (mU / L) between cases classified by TI-RADS as malignant and benign according to the histopathological diagnoses of the Bethesda scale.

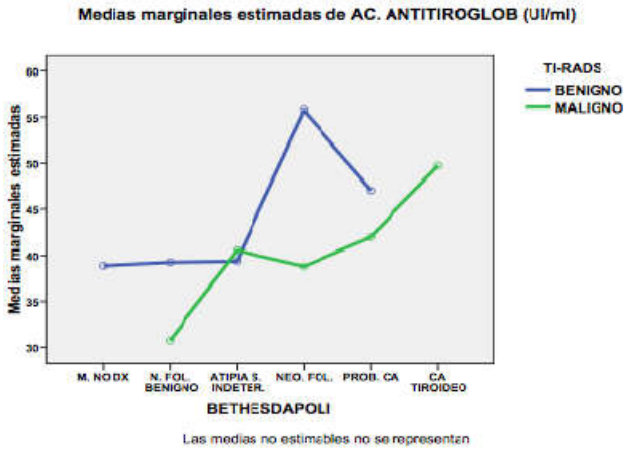
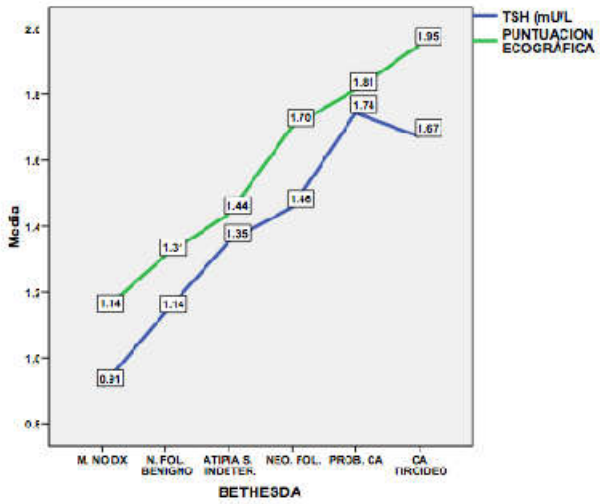


Figure 5. Comparison of anti-thyroglobulin antibody means (IU / ml) between cases classified by IT-RADS as malignant and benign according to the histopathological diagnoses of the Bethesda scale



Graph 6. TSH and ultrasound scores according to diagnoses of the Bethesda scale

whereas those above 0.40 IU / ml of anti-thyroglobulin antibodies have 1.8 [IC95% 0.8-4.3, p = 0.13] of malignancy. Taking the gold standard as a true reference, the reasons for the probability of malignancy increase as one goes from the low TSH intervals to the discriminating cut-off point of 1.63 mU / L or more, until reaching the corresponding confirmation area. at 2.13 mU / L up (Table 3). Now it is observed in the graph 6 with the two variables (TSH in natural values that go from 0.91 mU / L and the ecographic scores in logarithmic scale so that it is representable since the logarithmic scale is of base 10), it is observed that to each Bhethesda's diagnosis corresponds to an ascending ultrasound score from 1.14 for non-diagnostic sample to 1.81 for probable CA and 1.95 for CA and, at the same time, it is evident that TSH levels increase correlatively and this is because the ultrasound score is correlative (rho 0.465, p = 0.0001) to TSH.

DISCUSSION

Based on the findings found in this study, evidence is established between the correlation of serum TSH levels and the proposed TIRADS ultrasound report, which is not the case for anti-thyroglobulin antibodies levels. According to international literature, the correlation between these 3 variables has been very diverse, excluding one of them or associating the 3 for the prediction of development of malignant thyroid nodule, as it was in the study of the author Eun Sook Kim *et al.* in 2010 they published the study "Thyroglobulin Antibody Is Associated with Increased Cancer Risk in Thyroid Nodules", in which they studied 1638 patients with suspicious thyroid nodule observing a higher rate of positive levels of Ac Anti Tg (30.8% vs. 19.6%; <0.001) and elevation of thyrotropin (TSH) (2.5 2.8 mUI = L vs. 2.1 2.0 mUI = L; p 1/4 0.021) than benign nodules. Another study conducted by Ioannis Vasileiadis *et al.* in 2014, they published the study called "Thyroglobulin Antibodies Could be a Potential Predictive Marker for Papillary Thyroid Carcinoma", 854 pieces of thyroid were analyzed, noting that those nodules larger than 1 cm in size and serum levels requested preoperatively from TSH> 2.64 mU / ml were associated with the presence of papillary thyroid carcinoma, corroborated in histopathological study. In another study conducted by Sze Ling Wong et al., Published in October 2013, 930 pieces of thyroidectomy were analyzed, in which a strong association was identified between only the serum levels of anti-thyroglobulin antibodies with autoimmune thyroiditis for the development of Papillary Carcinoma. Thyroid (P = 0.0001). It seems that in several investigations, the constant identified when elevation of serum levels of thyroglobulin antibodies was observed, was either an autoimmune thyroid disease as a factor associated with risk of neoplasia or metastatic lymph node activity. In contrast, high levels of thyrotropin remained constant in the population without or with thyroid comorbidity, this being an important biochemical marker for patients without known thyroid disease. These serum findings were not found in association with the TIRADS ultrasound characterization, based on exhaustive review in the literature, being the combination of them, and more specifically for TSH and TIRADS, as predictors of malignant thyroid nodule in our rightful population.

Conclusion

US is valuable for identifying many malignant or potentially malignant thyroid nodules. Although there is some overlap

between the US appearance of benign nodules and that of malignant nodules, certain US features are helpful in differentiating between the two. With this in mind, the increase in serum levels of thyrotropin in our population allowed the two variables to be combined statistically for a better prediction of malignant thyroid nodules; Considering that internationally, there is still no consensus between acting in relation to this entity, the said indicators, an institutional level can be established, homogenizing and routing those patients who required puncture by aspiration with fine needle and the sea in the short, medium or long term. It is concluded that the combination of serum thyrotropin levels with an ultrasound characterization under the TI-RADS system, in right-holders of the Naval Hospital, were highly predictive of nodular malignant thyroid disease, conditioning a feasible diagnostic method for the evaluation of patients carrying thyroid nodule, thus avoiding, getting to perform unnecessary biopsies and surgeries.

Conflict of interests: The authors have no conflicts of interest

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