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Case Study

Clinical, Laboratory, Ultrasound and FNB aspects of thyroid nodules with calcifications

Abstract

Thyroid nodules are very frequent in the general population, with a low occurrence of malignancy among them. The present study was conducted on 517 patients of both sexes recruited at the Endocrinology Ambulatory of UNAERP, a secondary health service. The sample consisted of 464 women (80.97%) and 53 men (20.03%) with thyroid nodules ranging in age from 15 to 89 years (mean: 52.3 years; 51.8 years for women and 57.1 years for men). A total of 1808 nodules were investigated (1468 in women and 340 in men) and 67 lesions with calcification were detected, 14 of them classified as malignant. Standard ultrasound of the 67 nodules revealed that 53 lesions were hypoechoic, 7 were hyperechoic, and 7 isoechoic. Of the 14 malignant lesions, 8 (57%) were classified as hypoechoic, 3 (21.5%) as isoechoic, and 3 as hyperechoic (21.5%), with 6 of them containing microcalcifications, 4 containing macrocalcifications, 3 peripheral calcifications, and 1 a mixed calcification. TI-RADS classification of the 14 lesions showed that one (7.2%) was TI-RADS 3, 6 (42.8) TI-RADS 5, and 7 (50%) TI-RADS 6; being 92.8% of the malignant lesions TI-RADS 5 and 6. The BETHESDA classification for FNB of the malignant lesions was: 1 case as B2, 2 cases as B3, 1 case as B4, 5 cases (35.72%) as B5 (suspected as malignant), and 6 (42.72%) as B6 (carcinoma). Three of these 14 lesions (21.42%) showed invasion of the capsule and/or neighboring tissues. Among the malignant lesions, the TI-RADS and BETHESDA classifications were most associated with the diagnosis of malignancy in the anatomopathological exam of the excised lesions.

Introduction

The thyroid gland, the largest single endocrine gland in the human organism, is the first to form in the human embryo by about the twelfth week of life. The thyroid has a highly organized structure that can synthesize and store large amounts of its secretion products, i.e., the thyroid hormones triiodothyronin (T3) and thyroxine (T4). The gland consists of follicles, spherical structures of various sizes consisting of a single layer of epithelial cells – follicular cells –that limit a central lumen filled with colloid. The embryogenesis of the gland is completed by about the third month of pregnancy, with the rudimentary thyroid being bilobulated and linked by a ventral isthmus located between the second and third ring of the trachea and growing laterally even after birth [1]. The height of the follicular cells, the dimensions of the follicles and the quantity of colloid vary with the functional activity of the gland, which is predominantly controlled by pituitary (thyrotropin hormone (TSH) according to the circulating levels of thyroid hormones (negative feedback). Imbalance of the feedback axis alters the volume of the gland and the morphology of thyroid tissue (2). About 3 million follicles are present in the adult thyroid, forming the parenchyma of the gland, and about 20 to 40 follicles form the lobules. The stroma consists of connective tissue [2].

The thyroid, even more than other endocrine glands, shows morphological changes that accompany physiological modifications such as pregnancy and senility and may also exhibit other changes that do not reflect physiological variations. The shape of thyroid gland resembles a butterfly, but its name originates from the Greek word *tiros* (shield) [1]. In adult life, the thyroid weighs 15 to 25 grams, and has a high ability to change its volume in the presence of continuous or temporary stimuli. Due to continuous or repeated hyperplasia, this high growth potential gives origin to *goiter*, which may be diffuse or nodular [3].

Thyroid nodules are very frequent in the general population, usually with a low occurrence of malignancy, a fact that represents a challenge for the identification of nodules suspected of malignancy and for the decision about the necessary conduct [4-7].

Cases and Methods

A study was conducted on 517 patients of both sexes seen

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at the Endocrinology Outpatient Clinic of UNAERP, a secondary health service. The sample consisted of 464 women (80.97%) and 53 men (20.03%), ranging in age from 15 to 89 years (mean: 52.3 years, 51.8 years for women and 57.1 years for men). All patients had clinically diagnosed thyroid nodules, later confirmed by specific examination. A total of 1808 nodules were studied (1468 in women and 340 in men).

The study was approved by the "Plataforma Brasil" Ethics Committee (Protocol 96398818.0.0000.5498) and all patients gave written informed free consent to participate.

The clinical exam was reviewed by a single examiner who evaluated the aspect of the cervical region, the number, size and consistency of palpable nodules, nodule adherence to other cervical structures, palpation of locoregional adenomegaly, and hoarseness [5]. All subjects were submitted to the determination of TSH, free T4, free T3, thyroglobulin (Tg), Antithyroglobulin (Anti-Tg), Antithyroperoxidase (Anti-TPO) and Anti-TSH receptor antibody (TRAB) by eletroctrochemiluminescence. Normal reference values for adults are: TSH = 0.27 to 4.5 µIU/ml; Free T4= 0.8 to 1.9 ng/dl; Free T3 = 2.0 to 4.4 ng/ml; Thyroglobulin = 1.4 to 78 ng/ml; Anti TPO < 34 IU/ml; Anti Tg = < 116 IU/ml,TRAB = < 1.75 IU/L (4).

Ultrasound (US) examination was performed in patients with a palpable thyroid nodule (TN) or with a TN diagnosed during an echography exam of the cervical region due to other diseases, using a Samsung- Madison 8000 EX apparatus (Samsung Madison Co, Seoul, Korea) and the presence of calcifications was considered to represent a suspicion of malignancy [6,7].

Patients with 1 to 12 nodules were identified, with size ranging from 3 to about 80 mm.

Nodule vascularization was assessed and classified as absent or present and, when present, whether it occurred in a peripheral or central region or in both regions. The presence of predominantly or exclusively central vascularization was considered to represent a suspicion of malignancy [8-11].

The presence and type of calcification detected in the nodules was classified as micro, macro or peripheral, or as mixed (concomitantly central- micro or macro and peripheral) [12-16].

Ultrasound (US) examination also permitted the classification of the nodules according to the TI-RADS classification, which considers a markedly hypoechogenic nodule of imprecise limits and containing calcifications to be suspicious [17-19]. US examination was used to guide FNB of nodules larger than 10 mm, suspected for malignancy. FNB was performed on an ambulatory basis and the material obtained was examined after staining with hematoxylin-eosin and classified according to the BETHESDA criteria. TN classified as BETHESDA 3 were submitted to another FNB, and if necessary to a third FNB. TN with persistency of BETHESDA 3 classification and suspicion for malignancy in other exams carried out by us, and TN with BETHESDA 4, 5 and 6 classification were submitted to surgery because a molecular study was not available for them [20].

Results

The study was conducted on 65 patients (6 men and 59 women) out of 517 subjects with TN showing calcifications. Twelve of these patients had 14 nodules with the presence of calcifications and a diagnosis of malignancy. Their ages ranged from 23 to 85 years (group mean: 59.3 years), 45 to 85 years for men and 23 to 81 years for women (mean: 70.16 years for men and 56.91 years for women). The age of the patients with TN ranged from 15 to 89 years (group mean: 52.3 years, mean value for women: 52.3 years and mean value for men: 57.1 years). The mean age of the group with nodules with calcifications was 59.3 years, 51.18 years for women and 70.16 years for men.

Mean TSH values were 2.0 µIU/ml among patients with lesions without calcifications (BETHESDA 2), and 5.88 µIU/ml and 6.38 µIU/ml for nodules classified as BETHESDA 5 and 6, respectively. Among the patients with nodules containing calcifications and a diagnosis of malignancy (papilliferous carcinoma) the TSH value was 5.98 IU/ml for women and 3.61 µIU/ml for men. AntiTPO antibody titers were positive in 3 patients, AntiTg antibody was positive in 1 and both AntiTPO and AntiTg were positive in 2 patients with malignant nodules with calcifications.

Standard US examination of the nodules with calcifications revealed that 53 lesions were hypoechoic, 7 hyperechoic, and 7 isoechoic. Of the 14 malignant lesions with calcifications, 8 were hypoechoic (57%), 3 isoechoic (21.5%), and 3 hyperechoic (21.5%).

When vascularization of the 55 nodules containing calcifications were evaluated by the Lagalla-Chammas classification, 9 were classified as Chammas 2, 19 as Chammas 3, 2 as Chammas 4, and one as Chammas 5, all of them nonmalignant. Of those with calcifications and malignancy, 1 was classified as Chammas 1, 1 as Chammas 2, 7 were classified as Chammas 3 , 2 as Chammas 4, and 3 as Chammas 5. Overall, 3 lesions were classified as suspected of malignancy (3/31=10%; 2 Chammas 4 and 1 Chammas 5) and 5 as malignant (5/14=35.7%; 2 as Chammas 4 and 3 as Chammas 5) [8-11]. Of the 67 lesions containing calcifications, 14 were malignant, 6 of them containing microcalcifications, 4 containing macrocalcifications, 3 containing peripheral calcifications, and 1 containing mixed calcification [12-16].

TI-RADS classification mainly based on hypoecogenicity, undefined limits and presence of calcifications was applied to 53 lesions with calcifications not associated with malignancy and to 14 malignant lesions. Among the nonmalignant lesions, one was classified as TR-RADS 3, 8 (15.09%) were classified as TI-RADS 4, 30 (56.60%) as TI-RADS 5, and 13 (24.54%) as TI-RADS 6. Among the 14 malignant lesions, one (7.2%) was classified as TI-RADS 3, 6 (42.8) were classified as TI-RADS 5, and 7 (50%) as TI-RADS 6. TI-RADS 5 and 6 classification indicated suspected malignancy and corresponded to 92.8% of the malignant lesions [17-19].

The BETHESDA classification of the lesion material obtained by FNB of the malignant nodules was B2 in 1 case, B3

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in 2 cases, B4 in 1 case, B5 in five cases (35.72%) (Suspicion of malignancy, probable papilliferous carcinoma), and B6 in 6 cases (42.72%, malignant, papilliferous carcinoma) [20-30].

All 12 patients were submitted to exeresis of their lesions and 3 of the 14 malignant lesions (21.42%) showed invasion of the capsule and/or neighboring tissues. None of the excised lesions showed adenomegaly containing metastases of the carcinoma.

Discussion

Thyroid nodules are very frequent in the general population, being detected in 4 to 7% of the adult population investigated by palpation, in about 30% investigated by US, and in about 60% investigated at autopsy [3]. Three to 28% of excised nodules are malignant, with carcinomas being detected in 5 to 7% of patients diagnosed with TN. The differentiated nodules originated from a follicular cell, being classified as papilliferous carcinoma, the most frequent and least aggressive, and as follicular carcinoma associated with genetic mutations and more aggressive. Anaplastic carcinoma is a considerably aggressive undifferentiated carcinoma occurring in about 1% of cases, and is associated with the presence of various mutated genes. Medullary carcinoma originates from C or parafollicular cells and secretes calcitonin [1-3].

Thus, the major challenge is to determine which of these diagnosed nodules are malignant and require a specific conduct. Several investigative methods can be used to aid this clinical mission: measurement of hormones and antithyroid antibodies, standard US contemplating the echogenicity of the nodules in question, the presence of calcifications, the TI-RADS classification, and FNB with cytological examination of the excised material using the BETHESDA classification.

In the present study, 65 patients (12.57%) had nodules with calcifications, 14 of them (21.53%) associated with malignancy without any specific pattern. The age of the patients with TN ranged from 15 to 89 years (mean: 52.3 years), with a mean of 52.3 years for women and 57.1 years for men. The mean age of the group of patients with nodule calcifications was 59.3 years (51.18 for women and 70.16 for men) and was higher for the total group and for males without calcified nodules. This result suggests that TN calcification is not obligatorily associated with malignancy of the nodule and that the prevalence of TN calcification increases with age.

On average, TSH values were higher in nodules classified as BETHESDA 5 and 6 and in malignant nodules containing calcifications, but the anti-thyroid antibody titers were not correlated with malignancy or with the presence of calcifications (4). Hashimoto's thyroiditis is associated with thyroid lymphoma. Standard US examination showed that 57% of the malignant lesions were hypoechoic, in agreement with literature reports [23,31]. The presence of calcification in the TN studied here increased with age but was not associated with a characteristic signal of the presence of malignancy [32-35].

The study of vascularization of the 14 malignant nodules showed the presence of predominantly central (LAGALLA-CHAMMAS=4) and central (LAGALLA-CHAMMAS=5) vascularization in 9 (64.4%), a correlation considered to be moderate for the suggestion of malignancy. Of the 14 malignant lesions with calcification, 92.8% were classified as TI-RADS 5 and 6, this being the strongest correlation obtained in the present study.

Two literature studies have correlated BRAF mutation and molecular changes as being present in the genesis of calcified thyroid nodules and being associated with malignancy. However, neither study was later confirmed [36,37].

Conclusions

Thyroid nodules are very frequent in the general population, but have a low prevalence of malignancy. So far, there is no absolutely reliable exam for the diagnosis of malignant nodules, with the strongest correlation with malignancy being detected with the TI-RADS 5 and 6 classification (92.8%).

We are aware of the fact that the diagnosis of malignancy for a thyroid nodule is a puzzle and that each investigative exam performed corresponds to one of its parts. The more exams we can perform, the easier it will be to reach a correct diagnosis. However, if the number of exams should be limited for economic reasons, in our opinion, the option should be for ultrasound-guided thyroid FNB associated with (BETHESDA) classification, despite its limitations.

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