Hashimoto Thyroiditis and Thyroid Ultrasound: A Prospective Study

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Abstract

Purpose

We performed a prospective study in patients with positive thyroid peroxidase antibodies (TPOAb), to describe their ultrasound (US) patterns and the prevalence of thyroid nodules.

Methods

In 195 consecutive patients, with positive TPOAb, thyroid US was performed by the same physician and equipment and categorized into four echographic patterns (EP). We determined the prevalence of thyroid nodules and their etiology confirmed by cytology or histology.

Results

The median TPOAb was 526 IU/ml. EP1 or normal US was present in 9,7%; EP2 or early/indeterminate stage in 29,4%; EP3 or established thyroiditis in 45,4% and EP4 or advanced/late stage in 15,5% of the patients. TPOAb (median = 857 IU / ml) ($p = 0.001$), TSH and thyroid volume were higher in EP3. A higher degree of fibrosis was associated with TPOAb > 1000 IU/ml ($p = 0,003$). Thyroid nodules were reported on US at 47,2% of HT. Fine needle aspiration (FNA) was performed in 49/60 nodules. Cytology: *Bl*: 41 patients (83,7%), *B V*: 1 patient (2%): suspicious for lymphoma; *B VI*: 3 patients (6,1%) : Papillary thyroid carcinoma. Benign cytology was present in 56% of EP3 ($p = 0,048$).

Conclusions

Higher TPOAb, TSH levels, and thyroid volume were associated with EP3. Fibrosis correlated with TPOAb > 1000 IU/ml. In our population, benign nodules were associated with established thyroiditis patterns. The increased inflammation and immunological activity of Hashimoto thyroiditis (HT) could be a favorable environment for growth factors for benign nodular development.

Introduction

Chronic autoimmune thyroiditis (CAT) or HT is a chronic inflammation of the thyroid gland initially described more than a century ago. It is now considered the most common autoimmune disease [1, 2], as well as the most common endocrine disorder [3], and the cause of hypothyroidism [4, 5].

Currently, it is understood that the etiology of HT is multifactorial due to a complex interplay of specific susceptibility genes and environmental exposures [6]. The CAT diagnosis is established by a combination of clinical features, presence of serum antibodies against thyroid antigens (mainly to peroxidase and thyroglobulin), and appearance on thyroid US [7].

Some authors advocate the use of the US in cases of CAT [8, 9], while others find it useless [10]. The US features of CAT were described in several reports [11, 12]. In our prospective study, we considered the echographic patterns (EP) described by Ormeci et al [13].

A thyroid nodule is a common disease described in the thyroid field, and HT usually coexists with benign and malignant thyroid nodules [14–16]. Some reports describe a higher prevalence of benign nodules in HT than in the general population, which is usually attributed to stimulating factors such as TSH, IGF1, and local cytokines. However, there is still controversy whether CAT predisposes to malignancy [17–19].

The purpose of this study was to describe patients with positive TPOAb, their clinical, echographic, and nodular features. Additionally, our goal was to determine the prevalence of benign and malignant thyroid nodules according to EP.

Materials And Methods

The prospective single-center study included 195 consecutive TPOAb positive patients, with or without hypothyroidism. They were evaluated between February 2016 and January 2018 at the Endocrinology Division of Hospital JM Ramos Mejía in Buenos Aires, which is considered an iodine sufficient area. . In our hospital clinical practice, the measurement of TPOAb is consistently incorporated in patients who are evaluated for thyroid function. Patients who had undergone previous thyroid surgery or were diagnosed with Graves disease were excluded.

The patients' evaluation included clinical data (age, gender, thyroid function, medication), physical examination, and thyroid US, carried out by the same physicians and US equipment (Philips Envisor).

Serum samples were measured for thyrotropin (TSH), total T4 (T4), free T4 (FT4) and thyroid peroxidase antibody (TPOAb) using chemiluminescence IMMULITE 2000 (RR: TSH: 0.5-4.0 mIU /ml, T4 RR: 5 -11,5 ug/dl, FT4 RR: 0,8-1,4 ng/dl, TPOAb RR:<20 IU / ml)

Image analysis:

A. Sonographic characteristics were evaluated based on the features described in the different stages of HT [11,13,20].

The studied population was categorized into four groups according to their EP:

EP1: Normal US

EP2: Early-stage or indeterminate: homogenous or slightly heterogeneous echotexture, hyperechoic or slightly hypoechoic, smooth contouring.

EP3: Established thyroiditis consisted of cases with decreased parenchymal echogenicity, non-homogenous echo, and echogenic interlobular septa structure.

EP4: Cases of late-stage advanced thyroiditis with more hypoechoic parenchyma and marked non-homogenous echo texture, irregular contour, pseudo-nodules, and reduced size.

Thyroid volume (TV) was calculated using Longitudinal (Ld), transverse (Td), and anteroposterior (APd) diameters. They were expressed in cm for each thyroid lobe, to estimate the volume of the gland (US-TV) using the ellipsoid's formula.

The ultrasound physician (VC) assigned the EP to each patient but was unaware of the clinical history or thyroid treatment.

B. Evaluation of thyroid nodules: we studied thyroid nodules on CAT to establish their benign or malignant association.

The size of the nodule, echogenicity, margins, presence and type of calcifications, and shape (if taller than wider) were considered. FNA was performed according to ATA guidelines 2015[21]. The description of pseudonodules and nodules less than 5 mm were excluded. Moreover, cytology was reported by the Bethesda System [22] and histopathology when surgery was indicated.

Statistical analysis: it was done with SPSS 21.0: Student test, Kruskal Wallis for quantitative variables, and chi-square for qualitative variables.

Results

A total of 195 patients entered this study due to positive TPOAb. The median age was 49 years (range 17-79), of which 92.8% were female., The median TPOAb: 526 UI/ml (R: 45-1300), the median TSH: 3.21 mIU/L (R: 0.03-79), and the median time since HT diagnosis was 21 months (R: 0-360). It is important to remark that 72,3% of the patients were on LT4 therapy. Baseline characteristics are shown in TABLE 1.

A. We described the US echographic patterns which were always reported by the same physician and registered by the same US equipment:

EP1 or normal ultrasound was present in 19/195 (9,7%); EP2 or early/indeterminate stage in 57/195 (29,4%); EP3 or established thyroiditis in 89/195 (45,4%) and EP4 or advanced/late stage of thyroiditis in 30/195 (15,5%) of the patients (FIGURE 1).

TPOAb concentrations were higher in EP3 or established thyroiditis (median range= 857 UI / ml (53-1300) ($p = 0.001$) than the other EP, whose median (range) were: EP1= 605 IU / ml (140-1300), EP2= 331 IU / ml (45-1001), EP4= 422 IU / ml (46-1300) (FIGURE 2).

TSH measurement was higher in EP3 (median= 3.5 mIU/L) ($p = 0.007$). Although this TSH value was significant it could be biased since we must consider that TSH levels could be modified for different reasons: stress, transient disease, age, and treatments.

Thyroid volume was higher in EP3 (median=12, R: 3,37-110,58 ml) and lower in EP4 (median= 3,5, R: 1-10,6) when we compared all EPs ($p = 0.00$). (TABLE 2)

In addition, US thyroid characteristics were also taken into account: echo textures, contours, and fibrosis and their relationship with TPOAb activity.

Higher degree of fibrosis was associated with TPOAb >1000 IU / ml($p=0,003$). The absence of fibrosis and the mild degree occurred more frequently in the TPOAb <1000 IU / ml group. Other features to consider were that the heterogeneous echotexture and irregular contours did not correlate with TPOAb level.

We observed that 76,5% and 90% of patients with EP3 and EP4 respectively, were under LT4 therapy, compared to 38,9% with EP1(normal US) ($p = 0.001$). Both the median LT4 dose and the time elapsed since HT diagnosis were lower and earlier in EP1 (TABLE 3).

B. Thyroid nodules were reported on US in 47,2% of our patients (92/195).

In 60 patients (30,8%), the nodules were larger than 10 mm. The median nodules' size was 14,8mm (R: 10-32 mm). They appeared more frequently in female patients and patients older than 40 years ($p=0,01$). The US imaging echostructure of the 60 nodules was as follows: 13 (21%) hyperechoic, 11 (18.3%) isoechoic, 22 (36.7%) hypoechoic, 14 (23.3%) partially cystic. Furthermore, 45/60 (75%) were present in EP2 and EP3.

TPOAb levels in patients with nodules were similar to those without nodules with a median of 544 IU / ml (49-1301), but it was higher in EP3 and EP4 ($p = 0.04$).

FNA was performed in 49 of 60 nodules; in 11 nodules it was not possible to do so, due to patients' rejection or because they did not meet the indication criteria.

Cytological results : Bethesda (*B*): 4 patients(8,1%), *BI*: 41 patients (83,7%): 26 colloid nodules, 15 chronic thyroiditis; *B V*: 1 patient (2%): suspicious for lymphoma; *B VI*: 3 patients(6,1%): Papillary thyroid carcinoma(PTC) (Figure 3).

23/41 (56%) of cytologically benign nodules were present in EP3 vs 18/41 in the remaining EP ($p=0.048$).). Surgery was not indicated in benign cytology and did not show any malignant features in the follow-up procedure.

Malignant cytology: Category *B V*: Suspicious lymphoma was present in EP2.

B VI:PTC: 2/3 presented EP2 and 1 with EP1. AJCC/ TNM 8th edition for PTC: Patient 1: Stage 2, ATA risk of recurrent/ persistent disease: high risk; Patients 2 and 3: Stage 1, ATA: low risk.

Regarding the US features of malignant nodules, it was possible to observe that the microcalcifications and taller-than-wide shape predominated. ($p=0,001$).

Discussion

We undertook this prospective study, to determine in patients with positive TPOAb their EP, clinical features, and presence of thyroid nodules.

TPOAb positivity is a characteristic of autoimmune thyroid diseases [23] and represents an important tool for their diagnosis. Currently available laboratory techniques are more sensitive to detect these antibodies, which has probably influenced the increase in prevalence in different publications. The prevalence of positive TPOAb was 11.3% in the population study conducted in the NHANES III survey[24]. A Chilean study found the presence of TPOAb positivity in 9.8% of the patients who attended a medical check-up [25].

The cause of Hashimoto's thyroiditis is believed to be a combination of genetic susceptibility and environmental factors where the antibodies are produced mainly by a lymphocytic infiltrate in the thyroid gland [26], with a significant correlation between the degree of this lymphocytic infiltration and the antibody titer. This infiltration can be translated into a non-homogeneous pattern on thyroid US, however, it can be difficult to distinguish in the early stages.

The circulating concentration of autoantibodies (especially TPOAb and TGAAb), TSH, clinical signs, and thyroid US patterns are the criteria currently used for CAT diagnosis. FNA cytology and radioiodine uptake are not indicated [7].

It has been suggested that the presence of TPOAb may serve as a marker of future thyroid failure [27]. A high level of TPOAb confers a 2.1% annual risk of developing hypothyroidism, which is 18 times higher than the normal population [28] .

In our study we had a high median title of TPOAb (526 UI/ml), 72,3% of the patients were hypothyroid and were under LT4 therapy. Similar to what has been previously published in other articles, in patients with positive TPOAb, 19/195 (9.8%) had a normal US: EP1.

The highest TPOAb and thyroid volume occurred in the EP3 (established thyroiditis) group. The population had a high median title of TPOAb (526 UI/ml), 72,3 % were hypothyroid and were being treated with LT4 therapy.

In the pathophysiology of HT, thyrocyte destruction by antibody- or immune cell–mediated cytotoxicity leads to morphologic and microscopic changes, including enlargement of the thyroid, parenchymal infiltration by inflammatory cells, calcification, fibroblastic and vascular proliferation. Moreover, hypoechogenicity, pseudonodules and inhomogeneous parenchyma have been observed in patients with HT(Wu). These changes are the basis of the ultrasonographic characteristics. US is a noninvasive modality that provides information about the level of inflammatory activity [11] and the severity of thyroiditis [29].

The combination of US with clinical and serological assessments significantly improves sensitivity and specificity for CAT diagnoses [20, 30].

Half of the patients in our study had a characteristic Hashimoto's EP3 pattern, while 10% had normal EP1. The outcome probably due to the time of evolution and the LT4 treatment [31] is towards the atrophy that was observed in EP4.

Ultrasonographically, the greatest fibrosis occurred when TPOAb were above 1000 UI/ml. The other characteristics such as the heterogeneous echotexture and irregular contours did not show correlation. In advanced stages of US : EP3 and EP4, patients were hypothyroid and required a replacement of LT4 therapy.

Interestingly, we observed that 76,5% and 90% of patients with EP3 and EP4 respectively were under LT4 therapy, compared to 38,9% with EP1 (normal US) ($p = 0.001$). Both the median LT4 dose and the time elapsed since hypothyroidism diagnosis were lower and earlier in EP1.

It is still debatable whether all patients with autoimmune thyroid diseases are at increased risk for nodules and thyroid cancer or whether there are certain individual characteristics that increase this risk [32]. Although numerous studies have since investigated this hypothesis, nearly all were influenced by substantial selection bias, imprecise metrics, and/or retrospective analysis [17, 33–37].

It is widely known that many thyroid growth-stimulatory factors, such as TSH, insulin-like growth factor-1 and fibroblast growth factor, may be involved in the development of adenomatous lesions in young patients with Hashimoto's thyroiditis [38]. US is essential to differentiate true nodules from pseudonodules, which are an expression of the inflammatory infiltrate.

There was a 42.7% prevalence of thyroid nodules reported in the US of the population with CAT. The nodules were predominantly hypoechoic and appeared more frequently in the age group of 40–60 years.

Likewise, a high prevalence of benign nodules *BII* diagnosed by FNA 41/49 (83,7%) was observed:

Colloid goiter and HT, in EP3, a state of greater inflammation. We do not report *BIII* and *BIV* as described by Silva de Moraes et al [39] in patients with nodules and HT.

In 1893, Rudolf Virchow first proposed an association between chronic inflammation and the formation of cancer. Over the next century, this hypothesis has been verified through our understanding of a multitude of human illnesses. Classic examples of this adverse effect of inflammation on the risk of malignancy include the predisposition of patients with ulcerative colitis to adenocarcinoma of the colon and the impact of chronic hepatitis on the development of hepatocellular carcinoma [40, 41]. Several possible pathomechanisms have been proposed for the association of thyroid cancer and thyroid autoimmunity; (i) immunity is elicited towards pre-existing tumor cells leading to specific autoimmunity (tumor defense-induced autoimmunity), (ii) pre-existing autoimmunity leads to malignancy due to inflammation (inflammation-induced carcinoma), and also (iii) two diseases co-occur by common

causes. It remains a question whether the impact of autoimmunity is beneficial or harmful against thyroid cancer[42, 43].

Retrospective analysis of surgical series have strongly suggested an association between HT and PTC [44, 45]. Also, they were more recently reassessed in several studies conducted in consecutive patients submitted to FNA, who are believed to be less subject to potential selection bias of surgical series [35]. However, according to FNA studies, the link between PTC and HT seems less evident[18, 46] Rotondi et al [19] in a 10 year follow-up study of 510 patients with CAT, who presented a negligible risk of developing thyroid carcinoma nodules.

Resende De Paiva et al [17]from Denmark, identified 36 studies published from 1955 to 2016 (64.628 subjects), reporting an association between HT and PTC and thyroid lymphoma.

In the prospectively studied population with HT and nodules, surgical decision was taken into account based on cytological and clinical criteria according to ATA 2015 guidelines. Surgery was not indicated in benign cytology and no suggestive features of malignancy were found during the follow-up. Malignancy was diagnosed and confirmed in 2% (4/195) of the study: three PTC and one lymphoma. No higher prevalence of malignancy was found in our population.

Conclusion

The study that included patients with positive TPOAb, allowed us to observe different US patterns that represented different stages of HT.

The EP was reported by the same operator, who was unaware of the patient's clinical record and used the same US equipment. On US, the established thyroiditis pattern (EP3) and advanced late stage pattern (EP4) were present in 61% (119/195) of the patients. EP3 had the highest thyroid volume and TPOAb value. Both patients with EP3 and EP4 were hypothyroid in 76.5% and 90% respectively, and required a higher dose of LT4 than the normal US pattern (EP1). However, around 10% presented normal ultrasound (EP1), this could be early stages of CAT and whose evolutionary curve is uncertain.

Thyroid nodules were reported in 47,2% of the US scans, most of them were present in EP2 and EP3. In patients who underwent FNA 41/49(83,7%), cytology was reported as benign (*BII*). There was a correlation with EP3, a state of increased inflammation and immunological activity of CAT, suggesting that this could be a propitious environment for growth factors for benign nodular development. The prevalence of malignancy (2%), was not different from the references for the general population.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all participants included in the study.

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Tables

TABLE 1: Baseline features of the population

Population	N=195
Gender (F/M)	181/14
Age (years) X(range)	49 (18-79)
Age group distribution	
>18 <40 years	54 (28,7%)
≥40 <60 years	97 (51,6%)
≥60 years	37 (19,7%)
TPOAb(IU/ml) X(range)	526 (45-1300)
TSH (uIU/l) X(range)	3,21 (0,03-79)
Time since HT diagnosis (month) X(range)	21 (0-360)
Thyroid volume (ml) X(range)	9,18 (1,12-110,58)

TABLE 2: Characteristics related to Echographic Patterns

	EP1	EP2	EP3	EP4
TPOAb (IU/ml)	605	331	857 ☒	422
TSH(uIU/l)	3,06	3,55	3,54	1,71 ☒
Thyroid volumen(ml)	9,37	8,83	12,03 ☒	3,5
Nodules N(%)	8 (13,3)	14 (23,3)	31 (51,6) ☐	7 (11,6)

☒p<0,05

Figures

Figure 1

Endocrine

Figure 2

Endocrine

Figure 3

Endocrine