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Assessment of Clinical and Laboratory Limits between Hashitoxicosis and Graves' Disease

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Abstract

Background: Determine the clinical and laboratory features of Hashitoxicosis (Htx) and set standards that will help perform a differential diagnosis with Graves'Disease (GD).

Subjects and Methods: we evaluated 45 patients with Htx (Hashi-group) diagnosed between January/1995 and July/2019 with autoimmune hyperthyroidism and cytology compatible with Hashimoto's Thyroiditis (HT). The control group consisted of 51 patients with GD (Graves-group).

Results: clinical hyperthyroidism, free T4 (FT4), thyroid volume and need for antithyroid drugs were higher in the Graves-Group. Values of anti-thyroid antibodies and TSH were higher in the Hashi-Group. The definitive diagnostic criterion was cytology. Regarding the clinical course, 95% of the Hashi-Group had hyperthyroidism of short duration, while 84.3% of Graves-Group required radioactive iodine (RAI).

Conclusion: hyperthyroidism due to HT was milder than that associated with GD. In most citology was able to distinguish HT from GD and predict spontaneous resolution preventing unnecessary RAI.

Keywords: Graves'Disease, autoimmune thyroiditis, hyperthyroidism, Hashimoto's Disease

1. Introduction

Hashimoto's thyroiditis (HT) was first described in 1912 and is the most common form of thyroiditis (Hashimoto, 1912). This is an autoimmune disease that affects women more than men and can be associated with hypothyroidism, euthyroidism, or occasionally hyperthyroidism (Rathi et al., 2014). For centuries, Graves' Disease (GD) has been considered the main cause of hyperthyroidism (Davies, Larsen, & Mandel, 2011). However, from 1942 onward, histological studies of surgical specimens from patients with hyperthyroidism ascribed to GD demonstrated that, in some cases, it was actually Chronic Autoimmune Thyroiditis (CAT). Later there were several reports on clinical hyperthyroidism associated with the histology of CAT (Eden & Trotter, 1942; Doniach, 1959; Buchanan et al., 1961; Zellmann & Sedgwick, 1966; Fatourechi, McConahey, & Woolner, 1971). Clinically, 5% of the patients with CAT presented hyperthyroidism (DeGroot, 1996), and some authors refer to this atypical form of disease manifestation using the synonyms, "hyperthyroiditis", "silent thyroiditis with thyrotoxicosis" or "Hashitoxicosis" (Htx) (Davies et al., 2011).

Htx can occur during CAT, even after initial hypothyroidism, or, on the contrary, as the first manifestation, when the differential diagnosis with GD becomes a challenge (Schwartz, Bergmann, Zerahn, & Faber, 2013; Yamamoto et al., 1984). Cases of conversion from hyperthyroidism to hypothyroidism have been reported (Tamai et al., 1989), but the conversion from hypothyroidism to hyperthyroidism is considered very rare, one study reports three cases of autoimmune hypothyroidism that converted to hyperthyroidism requiring antithyroid treatment (Furqan, Haque, & Islam, 2014).

Both are known as autoimmune diseases of the thyroid, and their main lesion mechanism is associated in the former with massive destruction of the thyroid follicles via humoral and cellular immunity (Mazziotti et al., 2003) and, in the latter with the stimulation of thyroid hormone production via the occupation of thyroid-stimulating

hormone (TSH) receptors by stimulating antibodies (Ponto & Kahaly, 2012). However, studies have demonstrated that CAT and GD can have immunological abnormalities in common, and are part of a spectrum of autoimmune thyroid diseases, and may even occur in a same individual (Selenkow, Wyman, & Allweiss, 1984).

Thus ascribing autoimmune hyperthyroidism to GD was for a long time a convenient simplification, because it was considered a lot more frequent and that it associated with clinical markers such as exophthalmos and pretibial myxedema. However, the histological data introduced into this scenario the need to establish a clear diagnostic distinction between thyrotoxicosis due to CAT or to GD, which is important to select the therapy, avoiding surgery, radioactive iodine (RAI), or the prolonged use of antithyroid drugs (ATDs). However, up to the present time, few studies have considered this issue (Doniach, 1959; Buchanan et al., 1961; Fatourechi et al., 1971; Shane, Valensi, Sobrevilla, & Gabrilove, 1965). Some other methods have been used to diagnose the etiology of thyrotoxicosis, including the ratio of total triiodothyronine (TT3) to total thyroxine (TT4) (Carlé et al., 2013; Amino et al., 1981), the level of anti-TSH receptor antibody (TRAb) (Lytton & Kahaly, 2015; Tozzoli, Bagnasco, Giavarina, & Bizarro, 2012) and the ratio of free triiodothyronine (FT3) to free thyroxine (FT4) (Chutintorn & Bhasipol, 2016; Chen, Zhou, Zhou, Yin, & Wang, 2018). A recent study proposed that the FT3/TSH ratio may be a useful new index for the differential diagnosis of thyrotoxicosis, especially when associated with TRAb (Wu et al., 2021). However, clinical and laboratory comparison between Htx and GD outcomes by these methods are still inespecific.

Thus, the purpose of this work was to perform a prospective evaluation and comparison of cases of hyperthyroidism due to Htx and GD confirmed by cytologic examen, in order to determine the laboratory and clinical as well as outcome of these diseases and define aspects that will help in the differential diagnosis between them.

2. Subjects and Methods

2.1 Study Design, Ethical Consideration and Location

This is a prospective case-control study, in which the cases are the patients with thyrotoxicosis from Htx (Hashi-Group) and the controls are the patients with hyperthyroidism from GD (GD-Group). The patients were assisted at the Endocrinology outpatient clinic of the Federal University of Triângulo Mineiro (UFTM) and at the medical archives service of this university. This study was approved by the Committee of Research Ethics of the Federal University of Triângulo Mineiro under protocol number: 901.

2.2 Population and Sample

All patients collected blood for laboratory tests after the first visit, to measure the serum TSH, which was performed by the immunochemoluminometric method (ICMA) (IMMULITE® analyzer, commercial kits-Diagnostic Products Corporation, USA; RV: 0.38 - 4.50 mIU/mL) (Bronstein, Juo, & Voyta, 1994; Babson, 1991), FT4 by competitive immunoassay method (IMMULITE® analyzer, commercial kits-Diagnostic Products Corporation, USA; RV: 0.8 and 2.3 ng/dL) and anti-thyroid antibodies. The dosages of anti-thyroperoxidase antibodies (TPOAb) and anti-thyroglobulin (TgAb) were assessed by ICMA (IMMULITE® analyzer, commercial kits-Diagnostic Products Corporation, USA, TPOAb: RV <10 UI/mL; TgAb: RV <20 UI/mL) (Bronstein et al., 1994; Babson, 1991). All the patients of both groups, were also submitted to thyroid ultrasound (US), and fine needle aspiration biopsy (FNAB), 2 to 5 smears per patient, part fixed in alcohol at 95%, and part air-dried, stained using the modified Papanicolau technique – Shorr – and May-Grunwald-Giemsa stain, respectively). Thyroid ultrasound (NV: glandular volume 8-15 mL) was done using an ATL apparatus (Philips Medical Systems Company; Inc., United States), model HDI 1500, a 7.5 megahertz linear transducer, with a 3.0 cm focal point. FNAB was performed and specimens analyzed in all cases by a single pathologist with broad experience in thyroid cytology (Figures 1 and 2), whose differencial diagnostic criteria for CAT and GD were described by Davidson and Campora (1991).

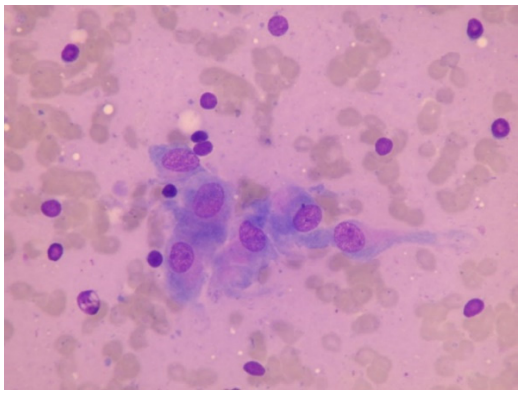

Figure 1. Hashimoto's thyroiditis. Askanazy type cells and lymphocyte infiltration (staining Grumwald-May-Giemsa)

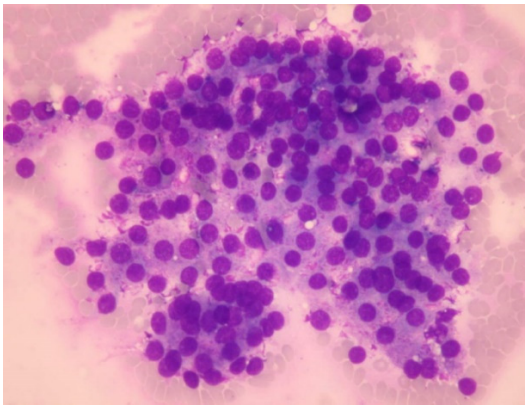

Figure 2. Basedow-Graves. Sheet of follicular cells with signs of hyperactivity (stained May-Grunwald-Giemsa)

Thyroid scintigraphy and uptake with ^{99m}Tc (obtained by gamma camera, 30 to 60 minutes after intravenous administration of pertecnetate ^{99m}TcO4, 1 to 10 mCi doses; NV:1 at 4%) was done in only a few patients due to the limitation to performing this exam at our service, as well as TRAb. Thyroid cytology was the standard test chosen to allocate patients into two groups.

For the Hashi-Group, 45 patients, 39 female and 6 male, aged 12 to 69 years (mean: 37 years) were selected according to the following inclusion criteria: diagnosis of autoimmune primary hyperthyroidism, based on suppressed serum TSH concentrations and elevated FT4 and positive anti-thyroid antibodies; cytopathologic diagnosis FNAB of CAT; and regular outpatient follow up. Fifty-one patients, 41 female and 10 male, aged 14 to 55 years (mean 33 years) with proved diagnosis of Graves' disease were selected to be compared to the Hashi-Group. They were seen during the same period and at the same outpatient clinic, with clinical-laboratory hyperthyroidism and a cytopathological diagnosis, and the patients were paired by age with the patients from Hashi-Group. The groups studied were compared according to clinical criteria, evaluation of thyrotoxicosis treatment and behavior of thyroid function in the clinical picture outcome.

The clinical criteria included symptoms of hyperthyroidism (nervousness, sweating, heat intolerance, palpitation, fatigue, weight loss, dyspnea, weakness, increased appetite, eye symptoms, legs edema, diarrhea, menstrual disorders) and signs (tachycardia, goiter, tremors of the extremities, skin changes, ocular symptoms such as proptosis, conjunctivitis, orbital edema, conjunctival hyperemia, eyelid retraction, atrial fibrilation, erythema of the palms, gynecomastia and thyroid murmur (Davies et al., 2011; Smith & Hegedüs, 2016).

The evaluation of the treatment of thyrotoxicosis and the comparison between the groups was done according to the following parameters: a) type of anti-thyroid drug used: b) initial dose of medication; c) time spent until the clinical compensation is reached; d) need for definitive treatment with RAI.

Finally, the comparison of thyroid function behavior in both groups studied was analyzed from the initial diagnosis of hyperthyroidism until the final day of this study.

2.3 Statistical Analysis

For the statistical analysis, the Kolmogorov-Smirnov normality tests were employed in order to verify whether the variables studied have a normal distribution. For comparisons between the groups we used the Mann-Whitney and Chi-squared test (X^2) with YATES correction. The analysis was performed using the SPSS versão 23. The level of significance considered was 5% or $p < 0.05$.

3. Results

The symptoms and signs of hyperthyroidism were represented at Table 1. Authough they are more frequent and intense in GD none of them were pathognomonic of one of the pathologies.

Table 1. Symptoms and signs of hyperthyroidism in patients with Hashitoxicosis (Htx) and Graves' Disease (GD)

Symptoms	Hashi-Group % (n)	Graves-Group % (n)	Signs	Hashi-Group % (n)	Graves-Group % (n)
Nervousness	80.0 (36)	97.0 (49)	Goiter	93.3 (42)	98.0 (50)
Sweating	Absent	90.0 (46)	Ocular signs and proptosis	6.6 (3)	90.2 (46)*
Palpitations	13.3 (6)	88.0 (45)*	Tachycardia	40.0 (18)	82.4 (42)*
Heat intolerance	17.7 (8)	88.0 (45)*	Extremity tremors	22.2 (10)	78.4 (40)*
Weight loss	13.3 (6)	80.0 (41)*	Hot and moist skin	17.7 (8)	78.4 (40)*
Dyspnea	22.2 (10)	72.0 (37)*	Palmar erythema	Absent	74.5 (38)
Weakness	62.2 (28)	70.0 (36)	Gynecomastia	2.2 (1)	Absent
Menstrual disorders	4.4 (2)	15.0 (8)*			

Chi-squared test (X^2) with YATES correction

*: $p<0.001$

Complementary exams were represented in Table 2. We found statistical differences when we compared the dosages of TSH, FT4, anti-thyroid antibodies, and glandular volume in the laboratory and complementary approach after the first visit. Despite statistical differences found it was not possible to determine any cutoff value among the variables that could distinguish one group from another helping the differential diagnosis, due to the greater superposition of the values found.

Table 2. Comparison of the complementary exams performed at the first visit on patients in the Hashi and the Graves Group

Tests	Hashi-Group	*n*	Graves-Group	*n*
TSH *(mIU/mL)*	0.02 (0.002 - 0.08)	45	0.002* (0.001 - 0.03)	51
FT4 *(ng/dL)*	3.0 (2.6 - 6.2)	45	5.6* (4.1 - 7.9)	51
TPOAb *(IU/mL)*	857.0 (11.3 - 4763.0)	38	123.0* (10.0 - 7516.0)	41
TgAb *(IU/mL)*	128.0 (20.0 - 5822.0)	38	120.0* (20.0 - 1131.0)	41
US total volume *(mL)*	16.2 (9.0 - 38.3)	45	26.90* (12.6 - 60.5)	51
^{99m}Tc uptake	1.0 (0.5 - 6.0)	$2^{\$}$/9	5.5 (4.5 - 7.0)#	$20^{\$}$/20

*: Mann-Whitney test $p<0.001$

#: Not compared

$^{\$}$: Increased uptake

As to treatment, among the 45 patients of the Hashi-Group, 82.2% (n = 37) used ATDs, and a β-blocker was necessary in 44.4% of the cases (n = 20). In the Graves-Group, however, all patients received initial treatment with ATDs in association with β-blockers. The ATD doses used (PTU and MTZ) were statistically larger in the GD-Group compared to the Hashi-Group ($p < 0.001$).

Analyzing the clinical outcome of the patients with Htx and GD, many differences were also found, as illustrated in figures 3 and 4 (Hashi-Group and GD-Group, respectively). The period during which the patient remained in thyrotoxicosis even using medication (during hyperthyroidism), was greater in the GD-Group (mean 22.4 months; variation from 11 to 48 months) compared to the Hashi-Group (mean 4.7 months; variation 3 to 20 months), $p<0.001$. Most of Htx patients had transient hyperthyroidism that spontaneously outcome to hypothyroidism (n = 25; 55.55%) or euthyroidism (n = 18; 40%). Only two of them had long term hyperthyroidism with need of ATD and RAI definitive treatment (Figure 3). In the follow up there was hyperthyroidism recurrence in 3 Htx patients but only 1 need RAI. For the other side, on GD-Group no patient spontaneously evolved to hypothyroidism and only 8 (15.69%) developed euthyroidism without need of definitive therapy (Figure 4).

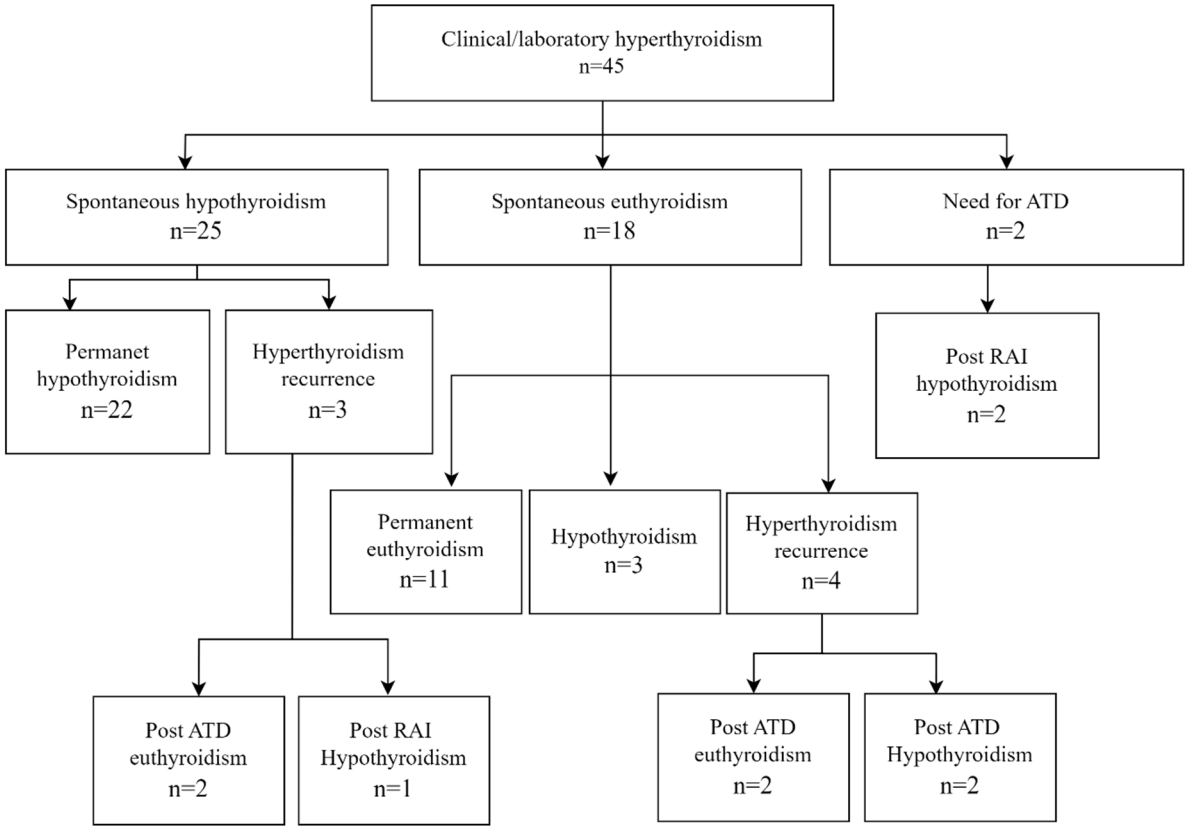

Figure 3. Clinical outcome of Hashitoxicosis patients (Hashi-Group); ATD: anti-thyroid drugs; RAI: radioactive iodine

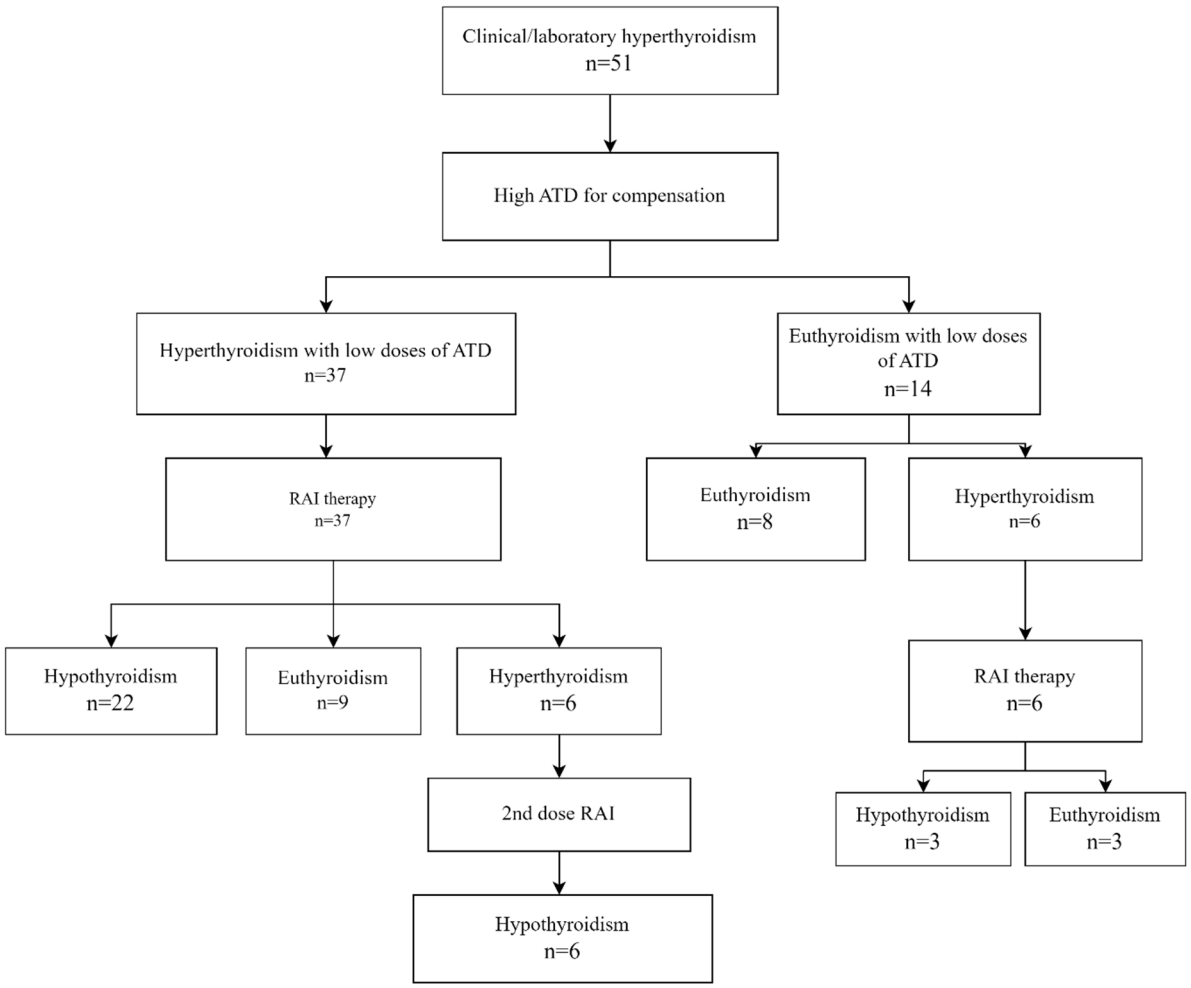

Figure 4. Clinical outcome for Graves' Disease patients (Graves-group); ATD: anti thyroid drugs; RAI: radioactive iodine

The FNAB specimens of the patients in the Hashi-Group who needed RAI due to persistent hyperthyroidism (n = 2) were reviewed, and after a clinical-cytological correlation the review was found to be compatible with GD associated with focal thyroiditis. Another FNAB specimens review was performed in 1 of the 3 patients who had a recurrence of thyrotoxicosis, even after spontaneous post-hypothyroidism, also due to the persistence of the picture for more than 1 year (15 months) and later RAI. After review, CAT associated with signs of follicular hyperactivity and characteristics similar to GD was detected, suggesting the coexistence of the two diseases in the same gland.

4. Discussion

In this study, a sample of 45 clinically hyperthyroid patients with cytological findings of CAT was compared to another sample of likewise hyperthyroid patients, but with a cytology compatible with GD, seeking limits that can help in the differential diagnosis between these two entities.

The signs and symptoms presented by the patients evidenced greater intensity and frequency of excess thyroid hormone manifestations in the GD group, especially regarding a compromised cardiovascular system and the presence of exophthalmos (Smith & Hegedüs, 2016).

However, none was pathognomonic for one or another etiology of hyperthyroidism, including ocular change which, despite being present in most GD patients, was not specific for this disease, since two patients of the Hashi-Group also presented this sign, confirming data from the literature that described this manifestastion in up to 5% of the cases of CAT (Burch & Wartofsky, 1993).

As to the laboratory tests, serum hormone determinations were more significant in the Graves-Group patients. More suppressed TSH values were associated with higher FT4, with a clear difference between the two groups.

Rubio et al. (1996) found higher levels of triiodotyronine ($p < 0.005$) in patients with GD compared to patients with Htx, while concentrations of FT4 and TSH did not show any difference ($p > 0.05$). In a recent study, thyrotoxicosis was also more severe in patients with GD than in patients with autoimmune thyroiditis. Serum levels of TT3, TT4, FT3, FT4, TPOAb and TRAb were significantly higher in patients with GD than in patients with autoimmune thyroiditis, while the serum level of TSH was significantly lower in patients with GD than in patients with autoimmune thyroiditis. Furthermore, the ratios of TT3/TT4, FT3/FT4, FT3/TSH, FT4/TSH, TT3/TSH and TT4/TSH were significantly higher in patients with GD than in patients with autoimmune thyroiditis (Wu et al., 2021).

Concerning the anti-thyroid antibodies, the concentrations of TPOAb and TgAb were much higher in the Hashi-Group, although it was not possible to establish a specific value for the differential diagnosis with GD. Several studies show a greater prevalence of anti-thyroid antibodies in patients with CAT compared to patients with GD (Doniach, Hudson, & Roitt, 1960; Ducornet, Moisson, & Duprey, 1991; Saravanan & Dayan, 2001).

However, few studies perform this comparison among groups of patients similar to those analyzed here. Hu, Liu and Lu (2003) evaluated 49 cases of GD and 22 cases of CAT coursing with hyperthyroidism in order to investigate the importance of the antibodies in the differential diagnosis between these two diseases. The authors found significantly higher ($p < 0.05$) serum values of TPOAb and TgAb in the group of patients with CAT (86.36% of positivity) compared to the GD-Group (48.98% of positivity), and the opposite occurred in the case of TRAb (83.67% of GD positivity versus 13.64% of CAT positivity). The determination of TRAb, although useful for the differential diagnosis of special forms of thyrotoxicosis, was not analyzed in this study because less than 50% of the patients performed this examen outside the UFTM which made the analysis of this data unreliable. Wu et al. (2021), indicated that TRAb level was the optimal parameter to distinguish patients with GD from those with autoimmune thyroiditis, among all thyroid-related parameters (excluding RAI and technetium-99m uptake). However a few researchers have demonstrated that approximately 10% to 30% of the patients with GD can present a negative TRAb (Schott et al., 2000; Costagliola et al., 1999) and that the same antibodies can be found in 10 to 20% of patients with destructive thyroiditis, and in up to 30 to 35% of patients with silent thyroiditis (Morita et al., 1990), reducing the capacity of the method to differentiate the etiology of thyrotoxicosis. It is also important to remember that the diagnostic accuracy of thyroid autoantibodies is more dependent on the type of assay used than is generally recognized. In a survey using 5 different assay kits, there was disagreement between positive and negative results for TgAb and TPOAb, and the correlation between kits varied widely (Nishihara et al., 2017).

As to scintigraphy and thyroid uptake with ^{99m}Tc, on the contrary of what had been expected, ie, a low uptake in the Hashi-Group cases, we find a normal uptake in almost half of the patients who were submitted to the test. In two patients, whose uptake was increased in this group, a concomitance with GD was later found. Of interest, among the cases where uptake was diminished, suggesting that it was a true destructive thyroiditis, one of them had a recurrence of hyperthyroidism with a need for RAI, and the concomitance with GD was also proved after the slide was revised. In the GD group the uptake was increased in all patients, suggesting that it is a good test for GD, but not for Htx, and thus it does not provide a definitive differential diagnosis in all cases of thyrotoxicosis.

As to the clinical outcome, our data suggest that the great majority of the patients with Htx evolve to spontaneous remission of the diseases while, conversely, most of the patients with GD evolve to a need of definitive treatment with RAI. Thus it is very important to distinguish these two diseases when planning treatment. The introduction of FNAB 40 years ago substantially improved the preoperative assessment of thyroid lesions due to its high positive and negative predictive value (Raza, Raza, Saeed, & Ahmed, 2006; Handa, Garg, Mohan, & Nagarkar, 2008). In one study, the most consistent cytomorphological features observed in fine needle aspiration smears of Hashimoto's thyroiditis were increased background lymphocytes, lymphocytic infiltration of thyroid follicular cell clusters, and Hurthle cells. Other associated features such as mild anisonucleosis, few giant cells and histiocytes, although not diagnostic, were observed in variable numbers on cytological smears and this is known to occur and this concludes that FNAB remains the "Gold Standard" for the diagnosis of Hashimoto's thyroiditis (Chandanwale et al., 2018). In another study that analyzed the cytology of TH, a high lymphoid/epithelial cell ratio was observed in 78% of the cases, and 74% of the cases had Hurthle cell alterations. Follicular atypia was observed in 36% of cases. The formation of lymphoid follicles was observed in 54% of the cases. Infiltration of follicular cells by lymphocytes, eosinophils and neutrophils was observed in 72%, 48% and 26% of cases, respectively. Plasma cells were observed in 18% of cases and this concludes that thyroid function tests and immunological tests cannot diagnose all cases of Hashimoto's thyroiditis and fine needle aspiration cytology remains an important diagnostic tool in the diagnosis of Hashimoto's thyroiditis (Rathi et al., 2014). The value of fine needle aspiration cytology (FNAC) and its role in the management of thyroid disease is indisputable. The FNAB also helps to prevent unnecessary surgery in case of thyroiditis (Suen & Quenville, 1983).

The prior clinical compensation of the patients with thyrotoxicosis, before the decision for definitive treatment with RAI, is part of the protocol to approach patients with hyperthyroidism in our service, in most of cases, what is according to the managements recommended by the Brazilian Society of Endocrinology and Metabolism (Maia et al., 2013). However, in the US RAI has been the most preferred therapy by physicians, but in recent years there has been a trend towards increasing the use of ATDs and reducing the use of RAI (Ross et al., 2016). In Europe, Latin America and Japan, there was a greater medical preference for ATDs (Wartofsky et al., 1991). The results of this work lead us to believe that using FNAB would allow the differential diagnosis between GD and Htx, and most Htx patients could be spared from RAI as a first choice of treatment, being enough to wait for the spontaneous resolution of the hyperthyroidism.

Another interesting observation regarding clinical outcome was the confirmation that episodes of thyrotoxicosis may occur even after spontaneous remission of the disease to hypothyroidism and, that in some of these cases there is truly a concomitance of the two diseases in the same gland (Tamai et al., 1987), which was confirmed by a new analysis of the FNAB in cases of atypical outcome. On the other hand, according to the literature (Leech & Dayan, 1998) spontaneous remission of hyperthyroidism of GD and an evolution to hypothyroidism or remaining euthyroid, may occur and it is very variable, being reported in 10 to 98% of the cases. Several factors are considered predictive of this remissions such as intensity of the lymphocyte infiltrate in the gland (Hirota et al., 1986; Mohlin, Nyström, & Eliasson, 2014), low TRAb titers, duration of treatment with ATDs, goiter size, baseline levels of triiodontyronine, patient age and gender (Ross et al., 2016; Tamai et al., 1987; Daukšienė, Daukša, & Mickuvienė, 2013). In this context the findings in our study raise a major question: could some cases of GD be mistakenly diagnosed, and their remission actually be ascribed to the gland being affected by CAT? This hypothesis sounds very plausible, since only patients whose FNAB indicated a picture of CAT presented true spontaneous remission. Most of the patients of the Graves-Group required definitive treatment with RAI. Thus, the fact that the thyroid is compromised by CAT alone when the disease is called Htx in the literature, or even in association with GD (concomitance of two diseases), when our group suggests the name of Hashi-Graves, could explain the remission of cases of hyperthyroidism initially diagnosed as GD alone.

This study has some limitations, such as the numbers of patients in each of the groups studied explained by the fact that not all patients agreed to undergo FNAC for research purposes. Another limitation was the impossibility of analyzing TRAb in several laboratories. However we believe that these limitations do not invalidate the results obtained.

5. Conclusion

In conclusion the results of this study suggest that thyrotoxicosis due to CAT is different from that associated with GD by its clinical features and the less severe outcome, shorter duration, smaller FT4 and TSH values, greater positivity of anti-thyroid antibodies, need for smaller doses of ATDs, besides spontaneous remission in most cases. Despite the differences found, these variables were not sufficient to establish the etiology of hyperthyroidism and, therefore, cannot be used for this purpose. As to the method used in this study to define etiology and treatment, FNAB, when performed by an experienced professional, was able to predict spontaneous evolution in 93% of cases of Htx, without the need for definitive treatment, avoiding the precipitous use of RAI. On the other occasions it was necessary to evaluate and await the clinical outcome to define the best definitive therapeutic management. In those cases there was a concomitance of the two diseases in a same patient, which led to diagnostic imprecision of FNAB.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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