

ANTITHYROPEROXIDASE ANTIBODIES (ATPO) IN HASHIMOTO THYROIDITIS: VARIATION OF LEVELS AND CORRELATION WITH ECHOGRAPHIC PATTERNS

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Antithyroidperoxidase antibodies (ATPO), antithyroid antibodies directed to thyroid follicular microsomes, are recognized as the test for diagnosis of Hashimoto's thyroiditis. The study tries to establish relationships between the ATPO and echographic picture in thyroiditis.

In 383 patients (15-85 years, 354 women and 29 men) the antithyroperoxidase assay was performed using ELISA technique, (N= 0 - 34 μ U/ml). Therefore, 185 patients had Hashimoto thyroiditis and 198 patients were excluded. The images obtained from all the patients and controls, classified in 7 patterns, showed that pattern #1 ("hypoechoic and pseudonodular") could be considered as pathognomonic for the diagnosis of Hashimoto thyroiditis: the predictive positive value was 95.61%. Five hundred and six evaluation moments echo-ATPO were correlated in both Hashimoto thyroiditis and control group. In patients with Hashimoto thyroiditis, 301 evaluations were performed, both immune (ATPO) and echographic. For all cases and patterns (36 degrees of freedom), χ^2 test was 77.35. **P value** was < 0.0001. When ATPO are high, pattern #1 was the most frequent, while for pattern #7 (normal), ATPO should be the lowest. The ATPO evolution can be considered mostly as unchanged during over one year observation. There is no correlation between the ATPO level, echographic pattern and thyroid function: the patients were in the same percent euthyroid and hypothyroid associated with similar echographic patterns.

In conclusion, this study shows a highly correlative relationship between the echographic pattern and ATPO levels in Hashimoto patients.

Key words: Autoimmune disorder, ATPO, Hashimoto's thyroiditis, thyroid ultrasound /echography, thyroid function.

INTRODUCTION

Antithyroperoxidase antibodies (ATPO) are considered as antithyroid antibodies directed to the thyroid follicular microsomes, i.e., antiperoxidase. It was

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argued that they represent both the pathogenesis of Hashimoto thyroiditis (as ADCC immune pathogenetic mechanism) and the way of identifying the disease (1-5).

The immune lesion of the thyroid could have several or only one imagistic shape. It was suggested that the echographic shape or echographic images in Hashimoto thyroiditis were somehow very typical for the disease (6-8). However, a standard echographic description of the immune thyroid disease is missing. A relationship between the pathogenical factor which generates thyroiditis (i.e., ATPO) and ultrasound shapes was made in only one published study (9) and in several previous communications (10,11).

This study tries to cover these aspects, bringing in front the problem of specificity, sensitivity and positive predictive value of some clearly described pattern of images recorded in Hashimoto thyroiditis and some comments related to immune associations. The analysis of ATPO evolution (i.e. fluctuation along the disease) will be presented, too.

MATERIALS AND METHODS

Hashimoto thyroiditis diagnosis

The diagnosis of Hashimoto thyroiditis was performed according to ATPO level: ATPO > 34 μ U/ml mean thyroiditis. The thyroid function and thyroid echography were related to immune pathogenesis.

Patients

From over 10 000 consecutive patients with thyroid disorders viewed in the last 5 years, in 383 patients (15 to 85 years, 354 women and 29 men) the antithyroperoxidase assay was performed using ELISA technique, normal range 0 - 34 μ U/ml (see later).

Two hundred fifty eight patients were euthyroid, 95 were hypothyroid and 45 were hyperthyroid. At the beginning of the study, no one was under thyroid substitution or antithyroid treatments. After diagnosis, hypothyroid patients received T4 therapy and hyperthyroid patients received either methimazole or carbimazole. Some of them received also a polarized, polychromatic, low energy radiation light Bioptron^R type (λ 480-3400 nm; the degree of polarization is 95% for the spectrum between λ 590 to 1550 nm and energy density 40 mW/cm²), according to Peretianu *et al* (12,13) known to activate the inflammatory immune responses.

Echographic description of the thyroid patterns

The echography was performed with an ALOKA 500 machine using a 7.5 MHz linear probe. The images obtained from all the patients and controls were classified into 7 patterns, according to Peretianu (9), as follows:

Type 1: hypoechoogenic and pseudonodular (Fig. 1 a) - "Symmetrically enlarged thyroid lobes with an inhomogenous hypoechoogenicity echotexture. The hypoechoogenicity could be described as important or marked. Areas of

hypoechoogenicity are bordered usually by hyperechogenic structures, described as fibrosis. In some cases the pseudonodule is surrounded by more hypoechoogenic or/and anechogenic rims, which generate a nodular shape. These anechogenic borders are probably of vascular origin and do not represent capsules for nodules (Fig. 1 b). Therefore, the areas rounded by hypoechoogenicity or anechogenicity could be described or viewed as pseudonodular. Frequently there could appear small calcifications”.

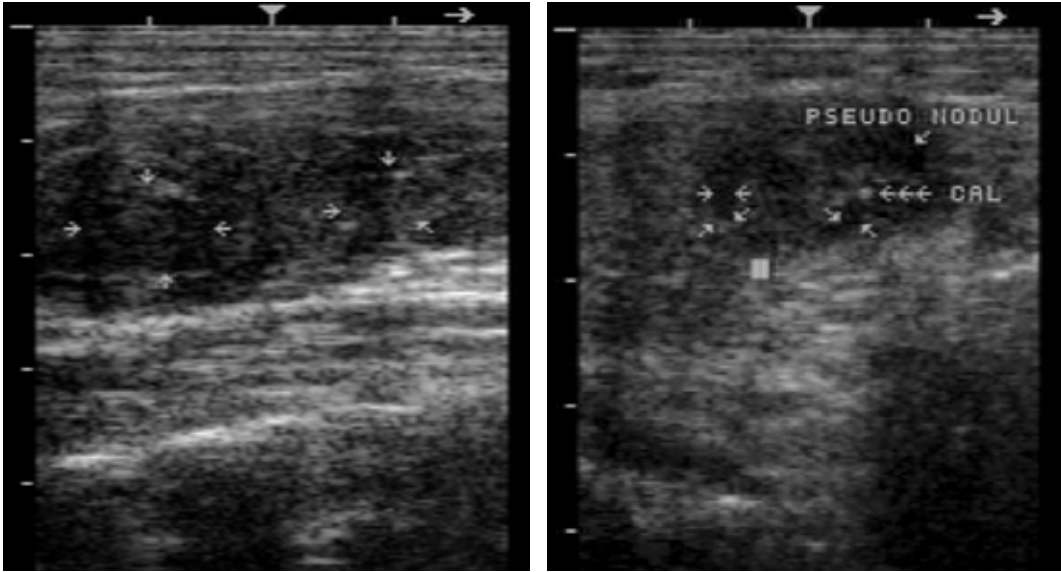


Figure 1 a. Pattern 1: Hashimoto's thyroiditis; the arrows in the left side mark the limit of a hypoechoogenic pseudonodule; the arrows from the right side mark small hyperechogenic linear areas (fibrosis). Figure 1 b. Very clear rim near a hypoechoogenic pseudonodule.

Type 2: only hypoechoogenic (Fig. 2)- “Enlarged or normal thyroid dimensions with hypoechoogenic background. No inhomogeneities and no anechogenic or more hypoechoogenic shapes. Sometimes, the thyroid is small”.

Type 3: only hypoechoogenic micronodular (Fig. 3) - “More than two hypoechoogenic nodules, each nodule with the length not more than 9 mm, are surrounded by a normal hyperechogenic fine granular background. The nodules are well limited, but without a clear capsule”.

Type 4: micro & macronodular (multinodular) (Fig. 4 a) - “More than two hypoechoogenic and/or anechogenic nodules and/or hyperechogenic and/or mixt nodules (Fig. 4 b), with a minimum of one nodule over 10 mm; the background is usually inhomogeneous, and some nodules are surrounded by a thick capsule of 0.3-1 mm.”

Type 5: inhomogeneous hypoechoogenic and pseudonodular (Fig. 5) - “Asymmetrically enlarged lobes, with a marked inhomogeneous echotexture. Foci

of a mixed or an increased echogenity are dispersed due mostly to fibrosis and scarring. Hypoechoegenities surrounded some areas generating pseudonodules”.

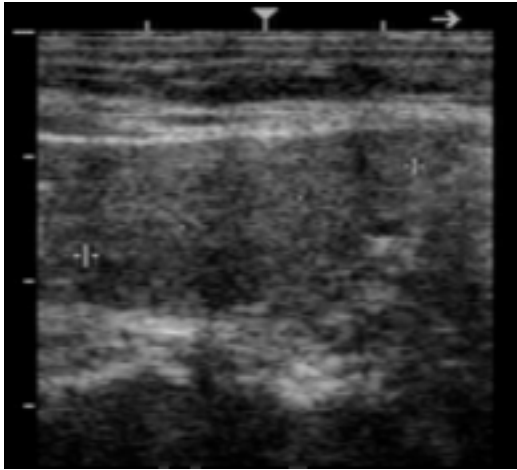


Figure 2. Pattern 2: Hypothyroidism nonHashimoto; diffuse homogeneous hypoechoicity.

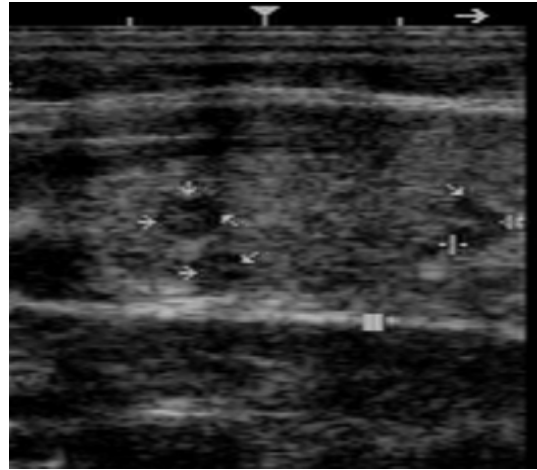


Figure 3. Pattern 3: Hashimoto's thyroiditis; the arrows mark small hypoechoic areas of 5-6 mm.

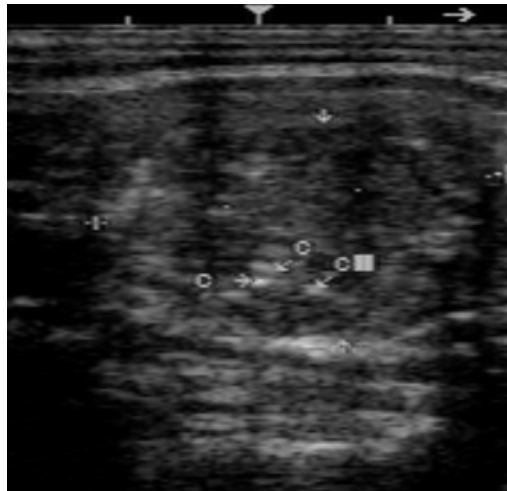


Figure 4 a. Pattern 4: Polynodular thyromegaly; macronodule with mixt structure in right lobe; C = calcifications. Figure 4 b. Almost anechoic nodule, in fact mixt.

Type 6: only anechoic micronodules (Fig. 6) - “More than two **anechoic** nodules, each nodule with the length not more than 9 mm, are surrounded by a normal hyperechogenic fine granular background. The nodules are well limited”.

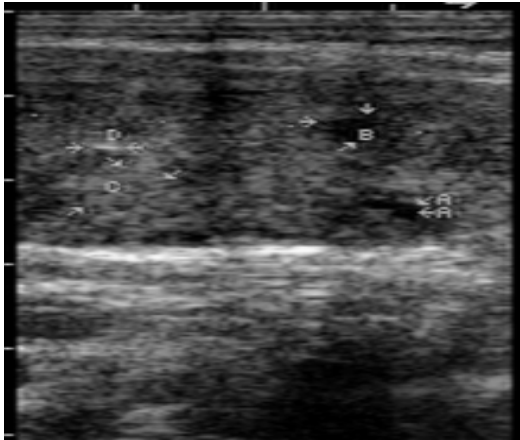


Figure 5. Pattern 5: Graves Basedow's disease; background with extremely inhomogeneous hypoechogenicity; A = tubular (vascular) anechogenicity, hypervascularization, B = anechogenic area, C = hyperechogenic pseudonodule; D = hyperechogenic linear area (fibrosis).

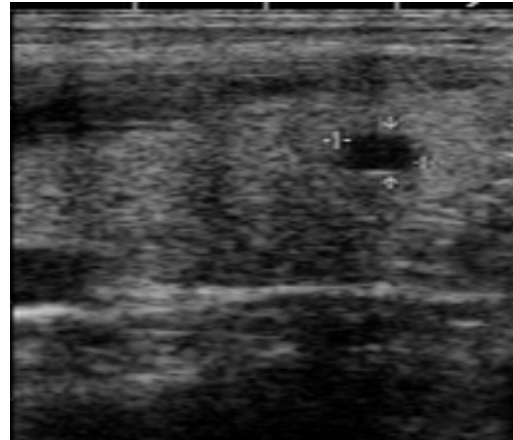


Figure 6. Pattern 6: Hyperechogenic diffuse homogeneous background; the arrows show small anechogenic area of 7 mm.

Type 7: normal (Fig. 7) - "The thyroid is diffuse hyperechogenic fine granular."

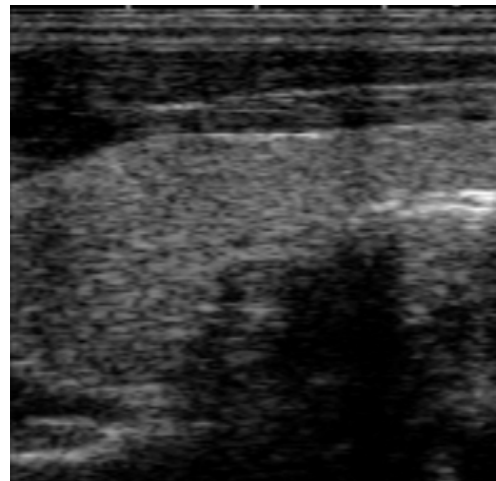


Figure 7. Pattern 7: Normal thyroid; hyperechogenic diffuse homogeneous background.

Antithyropoxidase antibodies

Antiperoxidase antibodies were measured in Elisa technique in 5 laboratories in Bucharest (Romania), using commercial kits, which showed the normal range under 34 μ U/ml.

The ATPO analysis was performed in some patients more than two times, in order to establish if treatments (or no treatment) had any effect on ATPO level. ATPO were repeated at 3 months, at 6 months and after one year since diagnosis.

Therefore, ATPO levels were shared into 9 levels, centred on the median value, suggesting a Gauss-Laplace slope, according to an original methodology (14,15). The correlations were registered in the statistical analysis.

Statistical analysis

The statistical value of the echographical images and correlation with ATPO serum levels were realized using the χ^2 test. The classical analysis of sensitivity, specificity, positive predictive value and accuracy was used for interpretation of the importance of echography images.

RESULTS

Thyroiditis diagnosis

According to ATPO criteria for diagnosis, 185 patients had Hashimoto thyroiditis and 198 patients had not such a disease; these later patients were considered as control group (table 1).

Many of the patients with Hashimoto thyroiditis showed thyromegaly, i.e. increase diameters of thyroid lobes, usually, over the limits of echographic probe (approximated at 4,5 cm). However, not a small group showed normal or small thyroid. When registered, thyroid atrophy (thyromicria) was pointed out (see later).

Table 1 Clinico-biological features of 383 patients with ATPO analysis

Parameter		Hashimoto thyroiditis	Control
Number		185	198
Sex	Women	173	181
	Men	12	17
Age (years)	Media	53.78	55.33
	Standard deviation	14.07	14.17
Thyroid function	Euthyroidism	95 (51.4%)	163 (81%)
	Hypothyroidism	71 (38.6%)	24 (11%)
	Hyperthyroidism	19 (10%)	16 (8%)

Correlation ATPO level - echographic pattern

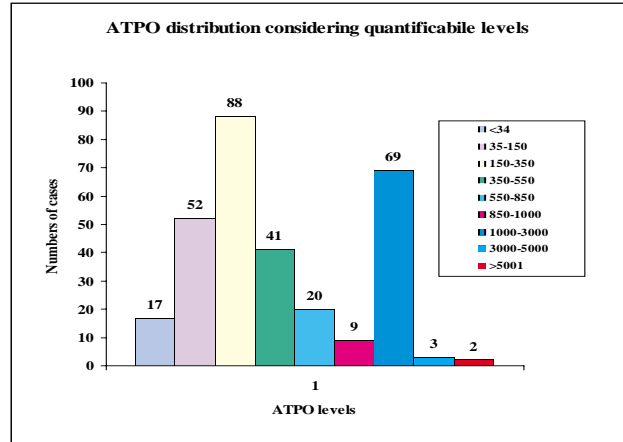
The main objective was to see if there are any correlations between the level of serum ATPO and the echographic appearance. For this reason, we performed a semi quantitative analysis using χ^2 test, after sharing the ATPO spectrum into 9 intervals, according to Onose (15) and Peretianu (14). The histogram distribution

ATPO versus echographic pattern in Hashimoto thyroiditis

simulated a Gauss-Laplace bell, centred on the average (~550 µU/ml): <34; 34-100; 100-350; 350-550; 550-800; 800-999; 1000-3000; 3000-5000 and > 5000 µU/ml.

The distribution suggests a real Gauss-Laplace bell (Fig. 8), with an unspecific tail for the interval 1000-3000.

Figure 8. ATPO histogram distribution.



Five hundred and six moments were correlated in both Hashimoto thyroiditis and control group (table 2). For all the patients (Hashimoto and controls) with all 7 patterns, χ^2 is $\gg 24.36$ and p value $\lll 0.00001$ (in fact it has 15 zeros after the point), with 6 degrees of freedom. These data mean that there could be interesting correlative relationships between the echographic patterns and ATPO levels; in these conditions, pattern #1 showed higher ATPO levels than the pattern #2, which showed higher ATPO values than the pattern #3, too. The last pattern, normal, # 7, is expected to have the lowest ATPO level.

Table 2 Thyroid echographic patterns in patients with Hashimoto's thyroiditis and control

Hashimoto thyroiditis		Control patients	
Pattern	Number	Pattern	Number
1	200	1	9
2	44	2	30
3	18	3	20
4	11	4	87
5	23	5	11
6	0	6	9
7	5	7	39
Total	301		205

Moments studied correlatively with ATPO levels > 34 µU/ml.

In patients with Hashimoto thyroiditis, during time, 301 evaluations were performed at the same time both immune (ATPO) and echographic. For all cases and patterns (36 degrees of freedom), χ^2 test is 77.35, P value is < 0.0001.

This also means that, when ATPO are high, pattern 1 is the most frequent. The analysis suggested that in pattern 7 (normal), ATPO should be the lowest.

From 57 patients with more than one ATPO analysis (see later), **only in 8 women (14%), the echographic pattern changes in time:**

In *ALLi*, the echographic pattern modified from #1 to #2 during decreasing fluctuant ATPO level from 201 $\mu\text{U/ml}$ (passing from 29 and 435) to 6 $\mu\text{U/ml}$.

In *ConTu*, the echographic pattern modified from #3 to #4 during decreasing fluctuant ATPO level from 108 $\mu\text{U/ml}$ (passing from 73 and 103) to 8.75 $\mu\text{U/ml}$.

In *VoiNi*, the pattern #1 changed to #5 after withdrawing Bioptron light therapy (BLT), when ATPO decreased from 880 to 563 $\mu\text{U/ml}$ and ATPO increased back to 610.5 $\mu\text{U/ml}$.

In *AIAI*, pattern #1 changed to #5 after BLT and after decreasing ATPO from 1000 to 407.5 (but passing through 309, 400, 1000 $\mu\text{U/ml}$, respectively);

In *BuEc*, pattern #1 changed to #2, when ATPO decreased from 1000 to 288 $\mu\text{U/ml}$, under levothyroxine treatment (even the patient was euthyroid !);

In *ConDo*, pattern #1 changed to #5, and ATPO increased slowly from 157 (through 184.5) to 197.5 $\mu\text{U/ml}$, under LT4;

In *VinEI*, pattern #1 changed, when ATPO were 273.5 $\mu\text{U/ml}$, 381.5 $\mu\text{U/ml}$, to pattern #2 under BLT, when ATPO levels were 300 $\mu\text{U/ml}$;

In *GodCr*, 29 years-old, with hypothyroidism, in which ATPO decreased after one year from 1000 to 31 $\mu\text{U/ml}$ (normal), through 1000 and 137 $\mu\text{U/ml}$, and pattern changed from #1 to quasi #7 (quasi normal) (Fig. 9); the patient received BLT 3 months with no change, and T4 one year.

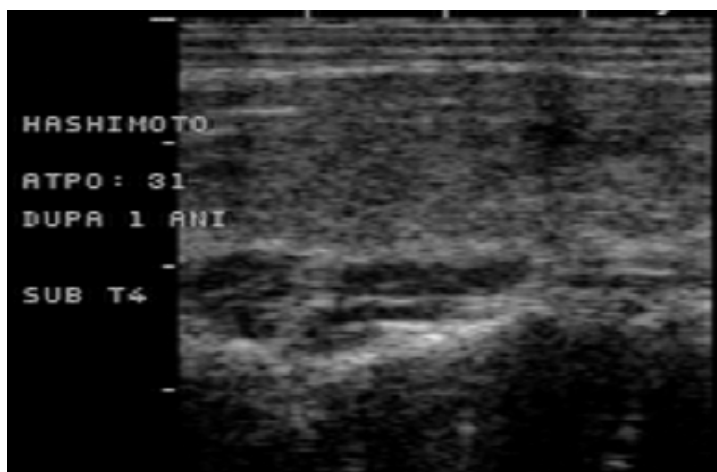


Figure 9. Case GodCr after one year: pattern quasi 7.

Analysis of specificity, sensitivity, predictive positive value and accuracy of echographic thyroid patterns in Hashimoto thyroiditis

For this analysis, we used data from 301 moments of 185 patients and the 205 moments of 198 control patients. From these data, percentiles of specificity,

sensitivity, predictive positive values and accuracy were calculated in Hashimoto thyroiditis for the proposed 7 patterns (table 4). Statistical analysis showed that, if pattern 1 appeared, it could be patognomonic for the diagnosis of Hashimoto thyroiditis; the argument could be the predictive positive value, close to 100% (i.e., 95,61%). However, many cases could escape the diagnosis, if we try to use only this test; the argument is the small value of sensitivity, around 70 % (i.e., 66.45%). High values of the specificity of patterns 2 (i.e., 85.37%) and 3 (i.e., 90.24%) lead to the idea that thyroiditis is possible with great probability when these patterns are described.

The high negative predictive value for pattern 4 (i.e., 87.88%) and the clinical context (anamnesis), suggest that in these patients the thyroiditis is improbable, as shown by others (16), too.

The accuracy of 100 % for pattern 6, which shows quasi-normal echographic shapes, is generated by the fact that no patient with this description has thyroiditis.

Table 4. Sensitivity, specificity, positive predictive value and accuracy of thyroid echographic patterns used for Hashimoto's thyroiditis

Pattern	1	2	3	4	5	6	7
Sensitivity (%)	66.67	14.67	6	4	7.33	0	1.33
Specificity	95.61	85.37	90.24	57.56	95.61	95.61	80.98
Positive predictive value	95.69	59.46	47.37	12.12	66.67	0	9.3
Accuracy (%)	78.26	43.28	40.12	87.88	42.69	100	88.64

ATPO evolution

The ATPO samples from Hashimoto thyroiditis patients showed an average of 553.39 μ U/ml, with an important variability, from 6.12 to > 5000 μ U/ml, SD: 808.56. In 29 cases, ATPO were analyzed more than twice (i.e., three or more). ATPO evolution could be described as:

Fluctuant (undulatory) pattern of ATPO level was observed in 19 patients (~65.5 %); In 14 cases, the treatments were both T4 and BLT, in 3 cases we did only T4 and in one case, the treatment was methimazole. Therefore, the ATPO evolution seems to be not dependent on specific treatment, either levothyroxine or BLT/PILER or both.

However, considering the last treatment, in 4 patients ATPO level decreased under BLT, comparing with only one case in which we gave levothyroxine.

only decreasing ATPO level was observed in 7 patients (24 %); 4 were under BLT/PILER, 2 were under T4 and one received carbimazole;

only increasing ATPO level was observed in 3 patients (~10.5 %). In additional 28 cases, ATPO were performed more than once (i.e., two times).

only descending pattern could be observed in 16 patients (57%); 8 (50% of them) were under BLT/PILER; only one was under levothyroxine; one received a

homeopathic treatment, one was under carbimazole and 5 received no treatment.

only ascending pattern could be registered in 6 patients (21.4%); 2 were under T4; 1 received methimazole and one was under BLT; the other two received no treatment;

no modified ATPO levels values appeared in 6 patients (21.4%); 2 were under BLT/PILER, one under T4, and 2 under no treatment. Considering the fluctuant pattern as non modified, and the sum of two subgroups (57 patients), ATPO level evolution could be considered as:

Unchanged / fluctuant in 25 patients (44%);

Decreasing in 23 patients (40%);

Increasing in 9 patients (16%).

Echographic patterns in relations with thyroid immune disorders; hyperthyroidism, thyroid atrophy and amiodarone associated with Hashimoto thyroiditis

a. In 19 patients (10.27%) with Hashimoto thyroiditis, we observed hyperthyroidism. In these cases, the most common echographic patterns were #1 and #5, both summing almost 75% (table 5). On the other hand, when pattern 5 is seen (23 analysis moments), hyperthyroidism was diagnosed in only 8 cases (35%). In one patient, the onset pattern #1 changes to pattern #5, and after that to pattern #3, under methimazole. In those analysis moments, ATPO were respectively: 45 µU/ml, 910 µU/ml and 900 µU/ml. In 9 patients, TSH receptor antibodies (TRAB) levels could be analyzed as diagnostic criteria for Graves Basedow disease (17):

In 8 cases (90%), TRAB levels were increased, suggesting the presence of both Hashimoto thyroiditis (ATPO increased) and Graves-Basedow disease (TRAB increased) which illustrates the concept of autoimmune thyroid disease;

In one case, TRAB was normal after treatment with methimazole (in this case, TRAB were not performed at the diagnosis time).

Table 5. Echographic patterns in Hashimoto' thyroiditis with hyperthyroidism and thyroid atrophy

Echographic pattern	Hyperthyroidism	Thyroid atrophy with hypothyroidism	Thyroid atrophy with euthyroidism	Amiodarone association
1	7 (37%)	2 (22%)	2 (22%)	5(71%)
2	3 (15.7%)	4 84%)	1 (11%)	-
3	2 (10.5%)	-	-	1 (1.4%)
4	-	-	-	1 (1.4%)
5	7 (37%)	-	-	-

b. In 9 patients with Hashimoto thyroiditis, the thyroid dimensions were small (Table 5); from these patients, 6 were hypothyroid (67%); the other 3 were euthyroid.

Hypothyroidism is associated with pattern #1 in 2 from 4 patients (50%) and

with pattern #2 in 4 from 5 patients (80%); that means that, when pattern #2 is associated with thyroid atrophy, hypothyroidism is very probable.

c. In 7 cases (3.8%), there was a history of amiodarone administration. Four patients were euthyroid and 3 were hypothyroid (2 patients with subclinical hypothyroidism). Over 70% patients showed pattern #1 (Table 5).

On the other hand, in controls there were 13 patients (6.5%) who underwent amiodarone, 3 with hypothyroidism, 1 with hyperthyroidism and 9 euthyroid (Table 6).

Table 6. Echographic patterns in NonHashimoto patients under amiodarone administration

Echographic pattern	Hypothyroidism	Hyperthyroidism	Euthyroidism	Total
1	-	-	1	1
2	3	1	2	6
3	-	-	1	1
4	-	-	1	1
5	-	-	1	1
6	-	-	-	-
7	-	-	3	3
Total	3	1	9	13

The difference between the two groups is: when hypothyroidism has appeared in Hashimoto, the pattern is mostly #1; when hypothyroidism has appeared in nonHashimoto, the pattern is always #2.

Association with other immune nonthyroid diseases

In 15 patients (8.1%), Hashimoto thyroiditis was associated with another nonthyroid immune disease (Table 7). On the other hand, in controls there were registered also 6 patients (3%) with nonthyroid immune disease (Table 7).

The difference seems to be significant: $\chi^2 = 4.76$ and **p** value = 0.029 (1 degree of freedom). That means that Hashimoto's thyroiditis associates more frequently than controls with other nonthyroid immune disorder.

The echographic pattern in Hashimoto's patients with other immune disorders is mostly #1 (with two exceptions, see table, discussed below).

The most frequent association seems to be with vitiligo: 5 patients (30%); and with rheumatoid arthritis: 3 patients (20%).

The most interesting association was observed in *NeaFI* (woman, 51 years) with cerebral vasculitis, Sneddon syndrome, cryoglobulinemia and sicca syndrome for 8 years, hepatitis C, discovered in 2004, in which viral C hepatitis level was overwhelming. In this woman, the thyroid echographic pattern was #7 (normal!) but ATPO were 49 μ U/ml.

In other 3 patients with Hashimoto thyroiditis, some endocrine associations could be described: acromegalia with NIDDM, Cushing disease with NIDDM and low IGF I, and IDDM.

Table 7. Immune associations with Hashimoto thyroiditis and control group

Hashimoto patients			Non Hashimoto patients		
Immune disease	Thyroid echographic pattern	Thyroid function	Immune disease	Thyroid echographic pattern	Thyroid function
Cerebral vasculitis with Sneddon sd, pulmonary fibrosis, hepatitis C, sicca sd	7	EUT	Systemic lupus erythematosus	7	EUT
Hepatitis	1	EUT	Insulin dependent diabetes mellitus	4	EUT
Dupuytren	1	HOT	Psoriasis	2	EUT
Psoriasis	1	<u>HIT</u>	Rheumatoid arthritis	7	EUT
Biermer anemia	1	EUT			
Rheumatoid arthritis	1	EUT	Rheumatoid arthritis	4	EUT
Shrap	1	EUT	Rheumatoid arthritis	7	EUT
Vitiligo	7	EUT			
Rheumatoid arthritis and lupus hepatitis	1	HOT			
Vitiligo	1	HOT			
Vitiligo	1	HOT			
Dermatitis	1	EUT			
Vitiligo	1	<u>HIT</u>			
Vitiligo	4 (!Sq TX)	EUT			
Rheumatoid arthritis and Sjogren sd	1	HOT			

DISCUSSION

Relationships between ATPO level echographic patterns and thyroid function

Our way of describing the echographic images from Hashimoto differs from others. Most of the authors described only hypoechogenic patterns. Some suggested more hypoechogenic degrees for Hashimoto thyroiditis: e. g from *mild to marked* (6-8) or from *first degree to third degree* (18). Others (19,20) suggested only one "diffuse hypoechogenic pattern", some timer with "heterogenic" shapes. Some recent studies investigated the hypoechogeneity only with "quantitatively gray scale" (21-26).

We observed more than one pattern; in Hashimoto's thyroiditis, we described 5 patterns (out of 7), without focusing on the value of echogenity, which, usually, is a subjective description. The main problem is to show if the patterns described by us could represent stages of immune lesions.

Some authors (27) affirmed that there is an overlap between echographic lesions and thyroid dysfunction, since there are patients with Hashimoto thyroiditis and normal echography. The last case was observed only in two patients in our series (see below). Thus, based on our results, we conclude that (with the underlined exceptions) there is no patient with Hashimoto thyroiditis without a modified echography.

On the other hand, only in pattern #1 description - diffuse pseudonodular shape - could the quantitative gray scale be analyzed. However, when there was a clear hypoechogenity (probable pattern #1), others (21-24) suggested that more hypoechogenity was correlated with more hypothyroidism.

Therefore, the most important result of this study is to affirm that there is a direct relationship and a significant correlation (!) between the level of serum ATPO and the specific echographic images described as specific patterns, mostly hypoechogenic and pseudonodular. The precise nature of this relationship could be related to the local echographic aspect of the immune reaction, since ATPO antibodies are considered as the main pathogenic factor in the ADCC process against thyroid cells (2,3). Another type of antibodies related to thyroiditis, such as TSH receptor-blocking antibody seems to be correlated to both the echogenic volume of the thyroid and the thyroid function (27).

However, this statement is not in contradiction with that which says that there is no direct correlation between the ATPO level and the specific pattern observed in Hashimoto's thyroiditis. That means that the nature of the immune process does not vary in time and can be viewed in the same manner during echographic observation.

At the same time it was suggested the negative correlation between the "level of hypothyroidism" and the ATPO level (25, 28): "When the maximum bioactive TPO antibody activity recorded was compared with echogenicity and thyroid status, there was a correlation between hypoechogenicity, elevated antibody activity and abnormal thyroid status ($r = 0.72$, $p < 0.001$)" (29).

In another clinical context (30), the importance of ATPO at the thyroid level was pointed out: it was shown that malignant nodules because of peripheral cellular impregnation could differentiate almost all of thyroid adenoma (benign nodules) with monoclonal antibodies developed against thyroperoxidase.

However, we observed that:

When pattern #1 was present, the thyroid function could be either euthyroidism or hypothyroidism and not hyperthyroidism (table 8); $\chi^2 = 6.76$ and p value = 0.02 (2 degrees of freedom). Furthermore, it means that there is no difference between hypothyroidism and euthyroidism patterns with echographic pattern 1. On the other hand, we did not observe any relationship, as others (31), between T4 administration in hypothyroidism and ATPO evolution (i.e., there is no decreasing ATPO when T4 was administered).

Table 8. Correlation between thyroid echographic pattern and the thyroid function at the diagnostic moment

Patterns	1	%	2	%	3	%	4	%	5	%	7	%	Total
Euthyroidism	62	65.26	12	12.63	8	8.42	7	7.37	4	4.21	2	2.11	95
Hypothyroidism	50	71.43	13	18.57	3	4.29	2	2.86	2	2.86	0	0	70
Hyperthyroidism	8	40	3	15	3	15	0		6	30	0	0	20
Total	120		28		14		9		12		2		185

When pattern #5 was observed, the thyroid function is significantly hyperthyroid, even if the number of cases is not big ($\chi^2 = 20.55$ and p value $\ll 0.0001$ (2 degrees of freedom)).

For the other patterns, no statistical significant relationship regarding the level of ATPO or the thyroid function was observed.

One of our patients (*PreDa*) recovered from hypothyroidism in which the serum ATPO level decreased, but the echogenic image did not change at all. The pattern #1 remained the same for more than one and a half year. This phenomenon was described by others (32), too.

Our study showed that ATPO evolved mostly fluctuant. It is known that fluctuant (undulatory) pattern of evolution of antibodies in immune diseases was pointed out for a long time (33). It is extremely possible that in Hashimoto thyroiditis the fluctuant pattern of ATPO evolution be the most widespread aspect.

Could the echographic patterns sustain the overlapping thyroid immune phenomenon?

The overlap among thyroid immune disease (primary hypothyroidism, Graves Basedow disease and Hashimoto thyroiditis) could be observed also in the echographic images in our study.

The pattern #5, observed also in Graves-Basedow's disease without thyroiditis ATPO-dependent (11 patients from 198 controls = 5%), could be viewed in

8 patients from 24 (33%) with Hashimoto thyroiditis. For these two diseases, the medical science succeeded to evidentiate the pathogenetic factors and to perform those analyses which diagnosed the diseases: ATPO for Hashimoto and TRAB for Graves-Basedow's disease.

Increased ATPO levels were described also in Graves Basedow disease (34), and TRAB could be observed in Hashimoto' thyroiditis (see above). On the other hand, many immune diseases are associated and are overlapping (35). For this reason, we considered that, in fact, in those patients there exist two immune thyroid disorders at the same time: both Hashimoto's thyroiditis and Graves-Basedow disease.

The similarity of echographic pattern #2 in some Hashimnoto moments (44 from 301 = 14.5%) and primary hypothyroidism without Hashimoto's thyroiditis in control patients (3 from 24 patients = 12.5 %) (see no echographic pattern difference between fig. 3 and 10) could be possible to be viewed also as an overlapping phenomenon.

All these statements could lead to another idea: all these three entities represent aspects of the same disease, because there is a real overlap of growth stimulating and growth blocking antibodies between Hashimoto and primary hypothyroidism (36), on the one hand, and there is a same ATPO activity in patients with both Graves' and Hashimoto's sera (37), on the other hand.

Related only to ATPO (not to echography), there were shown in this study also by others (7) that ATPO levels did not differ among patients with hypothyroidism and euthyroidism. However, not all agree with this statement (4).

In conclusion, our study shows that five echographic patterns can be described in Hashimoto thyroiditis. One of them, named "hypoechoogenic and pseudonodular" (pattern #1) could be considered as highly specific and most related to higher ATPO levels. This suggests that the other echographic patterns could represent evolutionary stages for the disease, including also the normal shape/pattern.

There seems to be no relationship between ATPO level and thyroid function in patients with altered pattern #1 compared with other patterns.

Considering the fluctuant pattern as non-modified, ATPO level evolution could be considered mostly as unchanged during over one year observation.

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