

# Some Clinical Aspects in Chronic Autoimmune Thyroiditis Associated with Thyroid Differentiated Cancer

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## ABSTRACT

**Background:** The coexistence of Hashimoto's thyroiditis (HT) with differentiated thyroid cancer (DTC) was reported with a heterogeneous incidence. The wide distribution of this association may be related to differences in the level of morphological examination, autoimmunity used criteria, patient selection, surgical indication, genetic background, geographical and environmental factors.

Some consider the coexistence of these two entities a coincidental one, others suspecting a causative link between these conditions.

**Methods:** This retrospective paper included 216 patients with HT, issued from an iodine-replete area. 21 cases of nodular HT were investigated by means of: thyroid functional tests (TFT), immunological determinations, thyroid ultrasonography (US) and cytological analysis.

All cases were operated because of different reasons: compressive symptoms and signs, suspicious sonographic features and certain cytological smears (malignant, indeterminate and non-diagnostic).

**Results:** The morphologic investigation revealed 9 patients with DTC and 12 cases with benign thyroid disease (BTD).

None of the US analyzed characteristics provided sufficient accuracy for the diagnosis of DTC in cases with HT. The preoperative cytological examination by means of fine-needle-aspiration biopsy (FNAB) showed a better sensitivity and specificity vs. US criteria.

**Conclusion:** The coexistence of HT with DTC represents a clinical reality with yet unknown significance. The difficulty of diagnosis imposes the corroboration of different types of investigations. The best diagnostic accuracy seems to be offered by thyroid US and thyroid cytological investigation.

**Keywords:** Hashimoto thyroiditis, differentiated thyroid cancer, thyroid ultrasonography, fine-needle aspiration biopsy of thyroid

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Article received on the 13<sup>th</sup> of March 2012. Article accepted on the 05<sup>th</sup> of November 2012.

## INTRODUCTION

**D**ifferentiated thyroid cancer (DTC) is the most common endocrine malignancy. The incidence of DTC increased worldwide over the past decades (1). Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) represent well-differentiated thyroid malignancies, accounting for approximately 95 % of all thyroid cancers.

The carcinogenetic process is a multifactorial one, implying different factors like: environmental exposure, loss of tumor suppressor genes and probably chronic inflammation.

The various thyroid autoimmune diseases (TAD) are very common for the general population, their incidence also showing a significant increase in the last decades.

Hashimoto's thyroiditis (HT) also called chronic lymphocytic or chronic autoimmune thyroiditis (CAT) represents a major entity of TAD.

The disease, an autoimmune inflammatory one, is characterized by widespread lymphocytic infiltration, fibrosis and gradual destruction of thyroid parenchyma. HT presents usually a diffuse goitre and a gradual loss of thyroid functionality. It associates circulating antibodies (Abs) against thyroid tissue antigens. The measurement in serum of two types of thyroid autoantithyroid antibodies (AT Abs): antithyroperoxidase antibodies (anti TPO Abs) and antithyroglobulin Abs (anti Tg Abs) is useful for the diagnosis.

The cause of HT is represented by a combination of environmental factors and genetic susceptibility (2).

Several reports have been published showing an increased incidence of malignant nodules associated with HT, based on retrospective analyses of surgical series (3-6).

HT and DTC (mainly PTC) share some epidemiological features like the relationship with dietary iodine and radiation exposure. Both diseases affect mainly women, showing also certain common molecular features.

The chronic inflammatory process may conduct to an inappropriate cell proliferation with subsequent neoplastic transformation.

Dailey and Lindsay reported first, in 1955 an increased association between HT and DTC (7). Since then, many studies confirmed this co-existence, not accepted by all (8,9).

The coexistence of these diseases recognizes variable incidence rates (10).

An increased risk of thyroid cancer was reported in the nodular forms of HT thyroiditis.

The aim of this paper is to present retrospectively and prospectively some aspects of the association between DTC and HT, trying to select valid criteria of malignancy vs. benignity, essential to a suitable therapeutic attitude.

The study attempts also to estimate the predictive value of ultrasonographic (US) findings along with fine needle aspiration biopsy (FNAB) in the diagnosis of malignant nodules in nodular cases with HT. □

## MATERIAL AND METHODS

**T**his retrospective observational study included 216 patients with HT, issued from an iodine-replete area, diagnosed in the Department of Endocrinology, County Hospital No 1, Timisoara, in the period 2006-2011. Patients with thyroid nodules were detected in 21 CAT cases (9.7%).

The inclusion criteria were represented by: both male and female patients, all age groups, with confirmed HT, defined by high titers of AT Abs and suggestive US features. In cases without detectable AT Abs in serum, HT diagnosis was established by thyroid US and FNAB.

All patients gave their informed consent. The subjects aged less than 18 years were included after their parents' consent. The study was approved by the local ethics committee.

For the entire group of patients, the age range was 15-74 years old, with a mean of  $48.56 \pm 13.52$  yrs and a female (F)/male (M) ratio of 205/11. The nodular cases of HT presented a mean age of  $52.3 \pm 16.3$  yrs and a F/M ratio of 17/4.

The diagnosis of HT was based on: clinical examination, TFT (TSH, FT4), significantly increased titers of AT Abs (anti TPO Abs, anti Tg Abs) and US.

Serum samples were tested for TSH (normal values: 0.46-4.67 mIU/L) and free T4 (reference values: 0.71-1.85 ng/dL), using ARCHITECT i2000SR (Abbott Diagnostics). Antithyroid antibodies were determined by CMIA, using Abbott Ax SYM System. The normal values were as follows: TPO Abs <12 IU/mL and Tg Abs <35 IU/mL.

Thyroid nodules, not always detected clinically, were evaluated by means of thyroid so-

nography, Tc99 uptake, scintiscan (selected cases) and FNAB.

US was performed using a Picker sonograph, equipped with a linear transducer of 7.5 MHZ.

The ultrasonographic analysis of nodules comprised the following aspects:

- the measurement of the largest nodular diameter (mm);
- the evaluation of nodular echogenicity (isoechoic, hypoechoic, hyperechoic);
- the character of nodular margins (smooth or blurred);
- the presence and aspect of calcifications (no, macrocalcifications. microcalcifications);
- the extent of cystic changes (none, <50%, >50%);
- the evaluation of nodular shape (the AP/T diameter);
- the nodular vascularization by means of Doppler sonography;

The irregular margins were defined as the occurrence of more than three lobulations on the surface of the nodule.

Microcalcifications were defined as punctuate hyperechoic foci <2 mm in size, regardless of any posterior shadowing.

The nodular shape was determined in accordance with the ratio of anteroposterior (AP) dimension to the transverse (T) one, as: round, tall (AP ≥ T) or flat (AP < T).

For FNAB aspiration it was used a 21-gauge needle. Cytological examination was done by the standard method.

The obtained cytological smears were classified as: non-diagnostic, benign, malignant, and indeterminate.

Surgery was performed in all cases, because of certain clinical aspects, suspect US features, and special cytological smears.

After surgery, all cases were examined morphologically. Nine patients presented different variants of DTC and the others various forms of benign thyroid disease (BTD). □

**RESULTS**

The clinical and laboratory data of cases with nodular HT are depicted in Tables 1 and 2.

The US features of nodular HT cases are represented in Table 3.

The cytological analysis of all operated patients revealed the following types of smears: malignant (4 cases), indeterminate (10 cases), non-diagnostic (3 cases) and benign (4 cases).

The indications for surgery are presented in Table 4.

Morphopathologically, DTC patients (9 cases) were represented by: papillary microcarcinomas (5 cases), multicentric papillary thyroid carcinoma (1 case) and papillary carcinomas, follicular variant (3 cases). □

| Parameter  | Cases with HT + NTD |
|--|---------------------|
| Number of cases                                    | 21                  |
| Mean age (± DS)                                    | 52.3 ± 16.3 yrs     |
| F/M  | 17/4                |
| Maximal diameter, mm (mean ± SD) (range: 15-31 mm) | 17.82 ± 7.53        |
| Palpable nodule                                    | 14 cases            |
| Non-palpable nodule (incidentaloma)                | 7 cases             |
| Apparent duration of the disease (months)          | 12 mo -72 mo        |
| Recommended surgical treatment                     | 21 cases            |
| Number of operated cases                           | 21                  |
| Duration of monitorization                         | 3-7 yrs             |

TABLE 1. Clinical data of patients with HT + NTD

| Parameter                                 | Cases of HT+NTD | Cases of HT without nodules | p       |
|---|-----------------|-----------------------------|---------|
| Number of cases                           | 21              | 195                         |         |
| Age (yrs) -mean±SD                        | 52.3 ± 16.3     | 47.65 ± 15.32               | 0.190†  |
| TSH (mIU/L)-mean±SD                       | 13.30 ± 7.47    | 22.87 ± 11.22               | 0.0002† |
| FT4 (ng/dl)-mean±SD                       | 0.99 ± 0.41     | 1.06 ± 0.34                 | 0.380†  |
| Positive anti TPO Abs                     | 18/21           | 159/182                     | 0.737‡  |
| Positive anti Tg Abs (significant titers) | 16/21           | 113/182                     | 0.238‡  |

TABLE 2. Thyroid functional tests and immunological data in cases of HT with and without thyroid nodules

† t-test  
‡ Fisher's exact test

| US feature                           | Malignant nodules (n = 9)           | Benign nodules   |
|--------------------------------------|-------------------------------------|--|
| Solid                                | -hypoechoic: 7/9<br>-isoechoic: 2/9 | -hyperechoic: 8/12<br>-hypoechoic:2/12<br>-isoechoic: 2/12 |
| Margins                              | -well defined: 6/9<br>-blurred: 3/9 | -blurred: 7/12<br>-well defined: 5/12                      |
| Halo sign                            | 2/9                                 | 6/12   |
| Sponge like                          | 0/9                                 | 6/12   |
| Calcifications (microcalcifications) | 5/9                                 | 0/12   |
| Solid with > 50% cystic areas        | 2/9                                 | 5/12   |
| Nodular Doppler vascularity          | heterogeneous                       | heterogeneous  |

TABLE 3. Sonographical features in nodular cases of HT

| Criteria                       | No of cases | % Cases |
|--------------------------------|-------------|---------|
| Compressive symptoms and signs | 4           | 19.04   |
| FNAB of malignant type         | 4           | 19.04   |
| FNAB of indeterminate type     | 10          | 47.61   |
| FNAB of non-diagnostic type    | 3           | 14.28   |

TABLE 3. Indications for surgery in nodular HT cases

## DISCUSSION

The prevalence of nodular goitre in HT is controversial, varying from 24% to 31% (11, 12). In our study the incidence of nodules associated with HT is lower as compared to the reported data. In the present study we selected only true nodular cases, excluding patients with pseudo nodules, frequently observed in HT.

The data regarding the incidence of the association between HT and DTC are heterogeneous. The communicated prevalence ranges from 0.5% to 38% (5,13).

For papillary microcarcinoma associated with HT, the prevalence is of 36.6% (14).

Although rare, numerous studies have reported a strong association between HT and primary thyroid lymphoma (15).

The large variation of prevalence between studies is probably due not only to the different environmental and genetic factors involved, but mainly to the various morphopathologic definitions of HT (16-18).

In our study, the prevalence of DTC among cases with nodular HT was of 42.8 %. Taking in account the whole group of autoimmune thyroiditis, the prevalence of DTC was of 4.16 %. A metaanalysis performed by SINGH showed that the incidence rate of HT is 2.77 times higher in cases with PTC than in those affected by BT. In patients with thyroid carcinoma, the incidence rate of association with HT is 1.99 times higher in those with PTC than in patients with other morphopathologic variants of thyroid carcinoma (19,20).

Although an association among morphologic, immunohistochemical, and biomolecular features of HT and PTC has been suggested, the real significance and possible clinical implications of this coexistence are not yet fully understood (4,21-23).

Some consider the coexistence of these two entities a coincidental one, others suspecting a causative and pathological link between these conditions (5,22,23).

The connection between HT and thyroid cancer is still debated. Many mechanisms have

been proposed to explain the link between these entities. Chronic inflammation that occurs in HT may trigger an immune response. Following the activation of different cellular factors, the stromal cells are constantly damaged. In the end, genetic abnormalities occur, with cell proliferation and neoplastic transformation (24).

In the process of thyroid tumorigenesis, several cell signaling pathways are altered. Phosphatidylinositol 3-kinase (PI3K)/Akt pathway is activated in thyroid cancer cells. The loss of tumor suppressor protein PTEN activity (which regulates the PI3K pathway) contributes to the neoplastic transformation (4). Other studies tried to explain the link between HT and RET/PTC rearrangements found in CAT: chronic inflammation could promote the rearrangement, or vice versa (24).

The nodular forms of HT impose complex investigations to elucidate the substrate of these lesions.

Analyzing the TFT and the immunological parameters, we noticed some significant differences between cases without and with nodules (see Table 2).

The US investigation of thyroid nodules offers useful data regarding the distinction between malignancies vs. benignity.

The main US features suspicious for a malignant tumor include: microcalcifications, hypoechogenicity, irregular margins, absence of halo, solid composition and predominantly central vascularity (25-27).

Certain sonographic features have been shown to be more predictive for benign nodules, including: a cystic component (>50%), a sponge like composition, hyperechogenicity and a thin and regular halo (17,28,29).

The analysis of US picture in the proven benign and malignant nodules showed certain pathological aspects of some used parameters. These regard the pattern of echogenicity, the occurrence of microcalcifications (for malignant nodules) and the sponge like appearance and the halo sign in BT (see Table 3).

On the other hand, some features did not show similarities to those seen in the general population. The benign nodules were not dominated by cystic elements and by well defined margins. In the same time, hypervascularity was not specific for malignant nodules. Similar aspects were communicated also by other authors (30,31).

On the basis of thyroid US aspects, guidelines for FNAB have been established by several professional organizations. Most recommend the cytological investigation of nodules with suspicious sonographic features (32,33).

For the malignant nodules, none of the recommended US characteristics studied provided sufficient accuracy for the diagnosis.

The cytological criteria imposing the surgery were represented by malignant, indeterminate and non-diagnostic smears.

The morphopathological analysis of malignant nodules was dominated by the following types of smears: malignant (4 cases), indeterminate (4 cases) and non-diagnostic (1 case). Taking into account the important incidence of carcinomas among indeterminate smears (34), we consider these high-risk cases, recommending surgical treatment.

The analysis of cytological and morphopathological examination revealed in micro PTC a predominance of indeterminate smears, in FVPTC mainly malignant smears and in the case with multicentric PTC a malignant cytology.

The morphological investigation of malignant cases showed some peculiarities of DTC with a HT background (Figure 1, 2 and 3).

Some difficulties of morphopathological analysis are presented in Table 5.

The prognosis of patients with thyroid cancer associated with autoimmune thyroiditis is still debated. Many studies confirmed that the coexistence of HT with DTC provides a better prognosis (35). The autoimmune process in HT implies a proliferation and accumulation of B lymphocytes, cytotoxic T cells, and macrophages in the thyroid tissue, but also in the lymph nodes. The cytotoxic T cells are involved in the destruction of the cancer cells (36). The cancer cells seem to be damaged by the autoimmune process. Furthermore, the thyroid-specific antigens might affect the cancer cells (35).

Our paper presents several limitations. The retrospective character of the study could lead to the exclusion of some cases with HT associated with cancer. Another limitation was the small number of patients with nodules included in the study. Also, we couldn't establish the risk of thyroid cancer in hypothyroid men versus women, because of the small number of male patients (n=4).

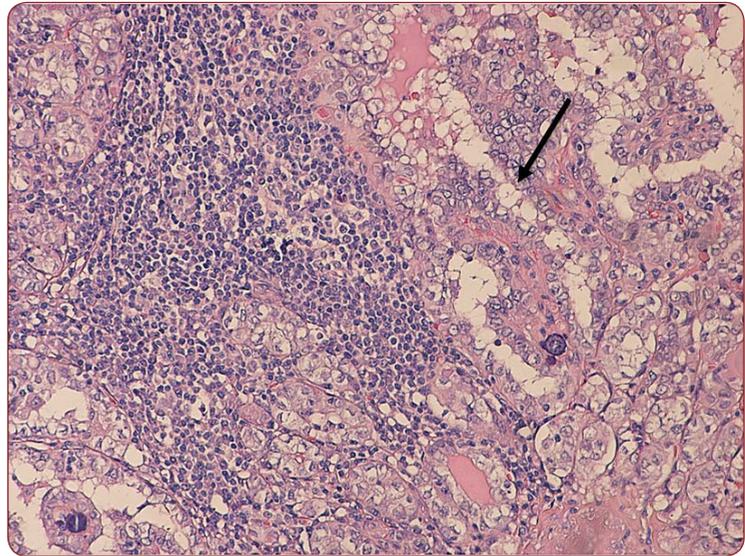


FIGURE 1. Classical PTC with HT (HE x 20).

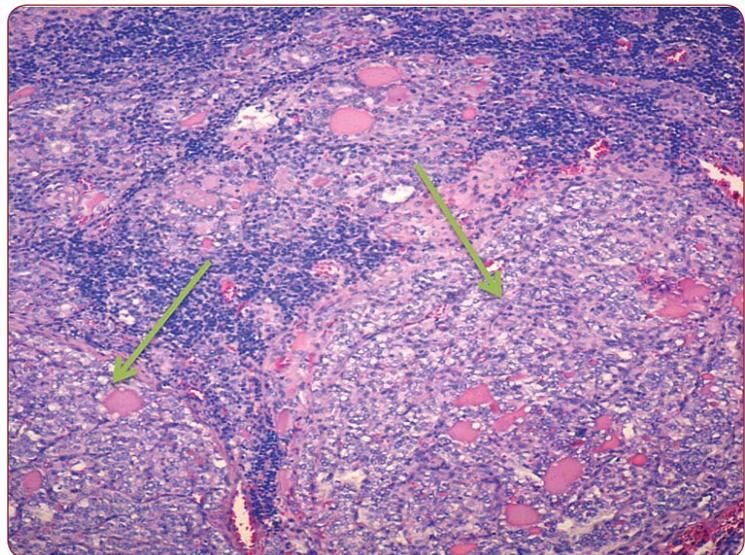


FIGURE 2. FVPTC and HT.

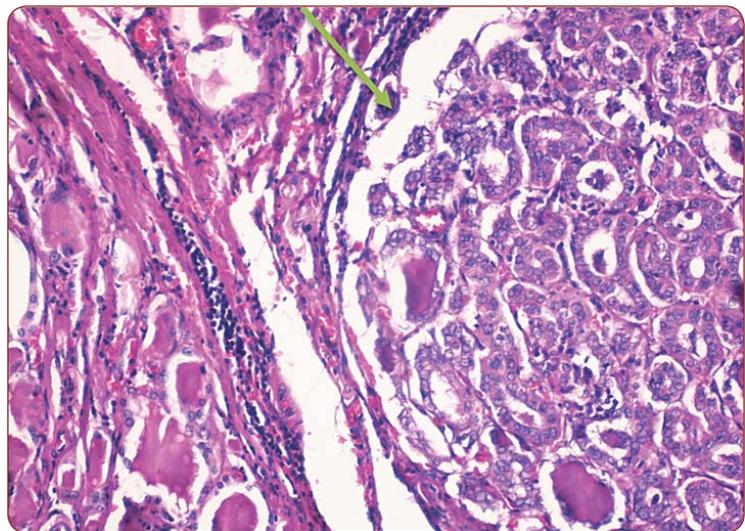


FIGURE 3. FVPTC developed in a HT.

| Type of lesions    | Difficulties of morphopathological diagnosis   |
|--------------------|--|
| PTC+HT             | - does not present special diagnostic problems;  |
| FVPTC              | - developed in a thyroid with HT may sometimes present a multicentric character  |
| Multicentric FVPTC | - presents some diagnostic difficulties due to:<br>→ reactive changes: the inflammatory infiltrate influences the nuclear aspect of oncocytes and follicular cells, which can mimic those of PTC<br>→ the nuclei are enlarged and clear, but without grooves, presenting a scattered disposition |
| FTC                | - does not present special diagnostic problems, being attested by vascular and capsular invasion.  |

TABLE 5. Peculiarities and difficulties of morphopathological analysis

In conclusion, the association of HT with DTC represents a clinical reality, which imposes complex investigations. The coexistence

appears in nodular cases of HT. The nodule might sometimes be an incidentaloma.

US investigation selects the cases that need FNAB.

No individual US parameter is suitable for preoperative diagnosis of thyroid carcinoma, but our malignant cases showed a higher prevalence of the following nodular US features: solid nodule, hypoechogenity, and microcalcifications.

The cytological investigation offers better diagnostic guide marks. Since some indeterminate and non-diagnostic smears proved to be histological malignant, we recommend surgical treatment in these cases.

The morphopathological analysis of DTC associated with HT was dominated by microcarcinomas.

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