CLINICAL STUDY

High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid autoantibodies

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Abstract

Objective: We assessed the association between thyroid autoimmunity and thyroid cancer in a retrospective series of unselected thyroid nodules submitted to fine-needle aspiration cytology (FNAC) to avoid the selection bias of surgical series.

Subjects and methods: Ultrasound (US)-guided FNACs were obtained from 590 unselected consecutive patients with single thyroid nodules and positive (ATA +, $n = 197$) or negative (ATA –, $n = 393$) serum anti-thyroid antibody (ATA). Cytological results were classified in three classes of increased risk of malignancy: low risk or benign (class II); indeterminate risk (class III); and suspect or malignant (class IV).

Results: A higher prevalence of class III (28.9% vs 21.4%, $P < 0.05$) and class IV (18.8% vs 9.2%, $P < 0.001$) and lower prevalence of class II (52.3% vs 69.5%, $P < 0.001$) were found in ATA + vs ATA – nodules respectively. By multivariate logistic regression analysis ATA + conferred a significant risk (odds ratio (OR): 2.29 (95% confidence interval (CI): 1.39–3.76)) for class IV cytology independently from age and sex. In 106 patients where thyroidectomy was carried out, thyroid cancer was found in 54/61 (88.5%) patients with class IV nodules (with similar positive predictive value for cancer in ATA + (96.4%) and ATA– (81.8%) nodules), in 6/31 (19.3%) of class III nodules (all ATA –) and in none of 14 class II nodules. Non-specific cytological atypias from hyperplastic nodules in lymphocytic thyroiditis probably accounted for the different prevalence of cancer in class III ATA + and ATA – nodules. Histologically proven thyroid cancer (mostly papillary) was then observed in a higher proportion ($27/197 = 13.7\%$) of ATA +, when compared with ATA – nodules ($33/393 = 8.4\%$, $P = 0.044$), but the significance of this finding is limited by the low number of class II nodules operated on.

Conclusions: The presence of ATA + confers an increased risk of suspicious or malignant cytology in unselected thyroid nodules. Since ATA + is not responsible for increased false-positive class IV FNAC, our study provides indirect evidence supporting a significant association between thyroid carcinoma and thyroid autoimmunity, although further studies with a different design are needed for a definitive histological proof.

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Introduction

The association of Hashimoto's thyroiditis (HT) and thyroid cancer (particularly papillary thyroid carcinoma (PTC)) has been suggested mostly on the basis of retrospective analyses of surgical series (1–7). In a large series of histological thyroid specimens, Hirabayashi and Lindsay (2) reported an increased prevalence (22.5%) of thyroid cancer in thyroid glands affected by HT when compared with glands without HT (2.4%). This finding was confirmed by later studies (4, 5). In particular, Okayasu *et al.* (5) provided clear evidence that the frequency of lymphocytic infiltration

was higher in patients with PTC, as compared with patients with adenomatous goiter or follicular adenoma; this result being independent of the ethnic origin of the patients examined. Further support for a significant association between PTC and HT was also provided by a recent meta-analysis (8). The main limitation of the above studies, however, was that they were carried out on patients who had had a thyroidectomy and were therefore subject to potential selection bias. Moreover, it is often difficult, on a histological basis, to differentiate lymphocytic infiltrate surrounding thyroid cancer from true lymphocytic thyroiditis (9); thus, is it still unclear whether thyroiditis is induced

secondarily by thyroid carcinoma or whether thyroiditis predisposes thyroid glands to the development of cancer. In contrast with surgical and pathological series, large population-based clinical studies (10–12) failed to show any significant increase of the incidence of thyroid cancer in cohorts of patients with HT followed for more than 10 years.

With the above concepts in mind, we decided to reassess the potential association between thyroid autoimmune disease and thyroid cancer from a different point of view. To this end, we retrospectively evaluated the cytological diagnoses obtained in a large number of consecutive unselected patients with thyroid nodules in relation to the presence or absence of associated serological features of thyroid autoimmunity. The validity of this approach was then assessed by comparing cytological results with histological results in patients who eventually received thyroid surgery.

Materials and subjects

Patients studied

During a 2-year period (from January 2002 to July 2004) a total of 590 unselected, consecutive patients with single or clearly prevalent thyroid nodules, referred to our outpatient service, were submitted to cytological examination performed on aspirates obtained by ultrasound (US)-guided fine-needle aspiration cytology (FNAC). All patients, (533 females with median age of 53 years and range 18–91 years; 57 males with median age of 58 years and range 26–85 years; female:male ratio, 9:1) also underwent a clinical (palpation), serological (thyroid function and anti-thyroid antibody (ATA) assays), morphological (US and color flow Doppler study) and scintigraphic (^{99m}Tc -pertechnetate scan) thyroid evaluation. All patients were euthyroid when FNAC was performed.

Conventional and color flow Doppler sonography

Thyroid ultrasonography and color flow Doppler study were performed using an Acuson Sequoia color Doppler system (Acuson Co., Mountain View, CA, USA) with an 8–12 MHz linear electronic transducer.

Thyroid function assays

All hormonal and antibody assays were carried out using commercial kits. Serum free thyroxine (FT4) and free tri-iodothyronine (FT3) were assayed by RIA (Technogenetics, Milan, Italy); thyrotropin (TSH) by ultrasensitive chemiluminescent assay (Ortho Clinical Diagnostic SpA, Milan, Italy). For ATA: anti-thyroperoxidase antibody (TPOAb) was assayed by RIA (Biocode, Liège, Belgium) and anti-thyroglobulin antibody (TgAb) by passive agglutination (Serodia, Fujiarebio

Tokyo, Japan). Normal values were as follows: FT4, 8.4–20.4 pmol/l; FT3, 4.3–8.6 pmol/l; TSH, 0.2–3.0 mU/l; TPOAb, <20 U/ml; TgAb, Neg. A total of 197/590 (33.4%) patients showed increased titers (corresponding to more than twice the cut-off) of serum ATA; this subgroup of patients was considered as unequivocally positive and was identified as ATA +.

Thyroid ^{99m}Tc -pertechnetate scintiscan

Thyroid scintigraphy was performed by means of a computerized gamma-camera equipped with a pinhole collimator (Elsint, SP4; Haifa, Israel) 30 min after i.v. injection of 110 MBq ^{99m}Tc pertechnetate. The scans were performed in anterior, left-anterior oblique and right-anterior oblique projections. Most patients showed a scintigraphic pattern characterized by a reduced uptake corresponding to a US position of prevalent thyroid nodules submitted to FNAC examination.

FNAC

US-guided FNAC was performed using 22–25 gauge needles attached to a 10 ml syringe. The smears (4–12 for each nodule) were immediately fixed with Cytotfix (Bioptica, Milan, Italy), and stained with hematoxylin–eosin (HE). According to standard criteria (13), we subdivided our cytological results as follows. Class I: not diagnostic or suggestive of colloid nodule (macrophages and colloid with no or rare follicular cells). Class II: benign nodule (monomorphic thyroid follicular cells without nuclear changes, abundant colloid and macrophages with or without hemosiderin); in this class were also classified the nodules fulfilling the typical cytological criteria for HT (monolayered sheets and small groups of follicular cells, sometimes with oncocyctic features, often with nuclear pleomorphism, admixed with or in close proximity to lymphocytes and occasional plasma cells). Class III: indeterminate follicular lesion (increased cellularity with microfollicular pattern, scanty or absent colloid, moderately pleomorphic follicular and/or Hürthle cells with mild nuclear changes). Class IV: suspect or frankly malignant (presence of atypical cells with abnormal nuclear shape, nuclear enlargement, nuclear polymorphisms and prominent nucleoli, or cellular nests loosely cohesive with marked overlap). In this class was included a cytological diagnosis of PTC on the basis of classical features (papillae and/or characteristic nuclear changes such as grooves and pseudoinclusions).

Surgical excision (total thyroidectomy) was carried out in 106 patients (61 with FNAC of class IV, 31 with FNAC of class III and 14 with FNAC of class II). Thyroid specimens were fixed with 10% buffered formalin. Each nodule was totally or subtotally sampled (with at least ten sections comprehensive of capsule) and included in paraffin. Serial slides stained with HE

were examined. The presence of benign or malignant neoplasias, as well as non-neoplastic lesions was identified by common criteria.

Statistical analysis

The association between cytological classes and the presence of ATA was evaluated using non-parametric tests (χ^2 with 0.05 as the probable significance level). Univariate associations between ATA, sex, age and cytological classes were tested using Student's *t*-test. The influence of covariates was analyzed by the logistic regression model, including all variables within $P \leq 0.15$ in univariate analyses, and tested by the likelihood ratio test. All calculations were performed using the SPSS statistical package version 11.5.

Results

Cytological findings

A total of 590 adequate FNAC specimens were considered for the statistical analysis. As shown in Fig. 1, the distribution of FNAC classes observed in ATA + patients was different from that found in ATA - patients. In particular, a significantly higher prevalence of class III (28.9% vs 21.4%, $P < 0.05$) and class IV (18.8% vs 9.2%, $P < 0.001$) nodules was found in ATA + when compared with ATA - nodules. In contrast, the prevalence of class II nodules was significantly lower (52.3% vs 69.5%, $P < 0.001$) in ATA + compared with ATA - nodules. Since a clear prevalence of ATA + was documented in females (185/498 = 37.1%) vs males (12/90 = 13.3%; $\chi^2 = 20.19$, $P < 0.001$), it was important to verify whether the association of ATA + with suspicious cytology was influenced by other potentially interfering variables such as sex and age. By univariate analysis, a significant association was confirmed between class IV cytology and ATA + (odds ratio (OR) 2.29; 95% confidence interval (CI) 1.39–3.76, $P < 0.001$), while class

IV was not significantly related to sex and showed a borderline association with younger (< 53 years) age ($P = 0.053$ by Student's *t*-test). As shown in Table 1, logistic regression analysis confirmed the significant association of class IV cytology only with ATA +.

Histological findings

To date, a total of 106 patients (mostly with class III and IV nodules) have undergone total thyroidectomy. As shown in Table 2, thyroid cancer was found in 54/61 (88.5%) patients with class IV cytology, while in the 31 operated patients with class III nodules, histological examination displayed a malignant lesion in about 1/3 of ATA - and in none of the ATA + nodules. No thyroid cancer was found in the 14 patients with class II nodules who were submitted to thyroidectomy. Table 2 also shows the positive predictive values of class IV cytology for thyroid carcinoma calculated in all operated patients. When ATA + and ATA - patients were analyzed together, the positive predictive value of class IV cytology for thyroid malignancy was 88.5, not significantly different from that calculated in ATA + and ATA - patients when considered separately. It is worth noting that, although the difference was not significant, the positive predictive value found in ATA + patients was higher (96.4) when compared with ATA - patients (81.8). Since class III is by definition indeterminate cytology, it was not possible to calculate either the positive or the negative predictive value for this class. The very small number of operated patients with Class II cytology prevented the calculation of the predictive values of negative cytological tests. Taken together, a total of 27/42 (64.3%) thyroid carcinomas were found in ATA + operated patients, a number higher but not significantly different from that found (33/64 = 51.6%) in ATA - operated patients. However, when the results of all patients that underwent FNAC were analyzed together, a higher cancer prevalence was documented in ATA + (27/197 = 13.7%)

Figure 1 Distribution of all cytological classes within ATA + ($n = 393$) and ATA - ($n = 197$) thyroid nodules. Class II, $n = 376$; class III, $n = 141$; class IV, $n = 73$.

Table 1 OR adjusted for age for class IV cytology calculated by logistic regression analysis in relation to detectable serum anti-thyroid antibody (ATA+) and age.

Variables	Odds ratio (95% CI)	P
ATA- and ATA+	2.29 (1.39–3.76)	<0.001
Age ≥ 53 years and age < 53 years	0.62 (0.37–1.03)	0.066

compared with ATA- (33/393 = 8.4%; $\chi^2 = 4.048$, $P = 0.044$) nodules. Regarding the type of thyroid cancer, the ATA- group displayed PTC in 27/33 (81.8%) patients and follicular thyroid carcinoma in 6/33 (18.2%) patients; in the ATA+ group almost all cases (26/27 = 96.3%) were PTC.

A puzzling finding resulting from the comparison of cytological and histological results was the different rate of cancer found in ATA+ and ATA- class III nodules. Accurate revision of all class III cytological smears from operated patients failed to identify any peculiar feature that could explain this difference. In particular, since the presence of lymphocytes or Hürthle cells may represent a potential source of error in FNAC interpretation (14), we looked at the presence/number of lymphocytes and Hürthle cells in ATA+ and ATA- Class III FNACs. The prevalence of Hürthle cells was not significantly higher in ATA+ (3/9 = 33.3%) when compared with ATA- (4/22 = 18.2%) nodules and lymphocytes were never observed. To further clarify this issue, we compared the histological diagnoses of class III ATA+ and ATA- nodules of operated patients. As reported in Table 3, the main difference found was represented by the higher frequency of follicular neoplasias (15 (9 adenomas and 6 carcinomas)/22 = 68.2%) in ATA- nodules when compared with ATA+ nodules. The latter was mostly represented (6/9 = 66.6%) by hyperplastic adenomatoid nodules with atypical microfollicular pattern, in a background of lymphocytic thyroiditis.

Discussion

Our findings obtained in a large series of unselected thyroid nodules that underwent FNAC, displayed a

higher prevalence of suspicious cytology in patients with positive serum ATA when compared with those without detectable serum ATA. Logistic regression analysis showed that serum ATA conferred a significant risk of suspicious cytology independently of other potentially confounding factors such as age and sex, in spite of a markedly increased frequency of ATA+ in females. This result is in keeping with several previous pathological studies, as discussed in the Introduction (1–8). A limitation of our study is certainly represented by the fact that positive serum ATA does not necessarily mean lymphocytic thyroiditis; but, an important and, to the best of our knowledge, unique feature of the present investigation is the lack of any selection bias in the series studied. However, the finding of a significantly increased prevalence of suspect cytology in thyroid nodules associated with positive ATA can not be considered as evidence suggesting an association between thyroid cancer and thyroid autoimmunity in the absence of histological confirmation. It is in fact recognized that FNAC presents some potential sources of error when performed in glands harboring autoimmune thyroiditis (15, 16). Follicular cell changes associated with HT can be mistaken for thyroid neoplasm resulting in false-positives. On the other hand, a neoplasm can be overlooked based on the cell population present in a sample from HT, resulting in false- negatives (16–18).

In our series, the histological examination of the subgroup of patients that underwent thyroidectomy excluded the fact that thyroiditis could account for false-positive cytology in nodules with the highest cytological risk (class IV). Indeed, class IV cytology had similar positive predictive values for thyroid carcinoma in ATA+ and ATA- nodules. In fact, the positive predictive value of class IV cytology was higher (96.4) in ATA+ when compared with ATA- nodules (81.8), although the difference was not statistically significant. When ATA+ and ATA- operated nodules were analyzed together, class IV cytology gave a positive predictive value of about 90%: thus, assuming that 9/10 class IV nodules are actually thyroid carcinomas, the extrapolation of the increased risk of suspicious cytology shown in our ATA+ patients provides indirect evidence of increased risk of malignancy in thyroid

Table 2 Distribution of benign and malignant histology in ATA+ and ATA- thyroid nodules from patients that underwent surgery: comparison with cytological classes and predictive value with 95% CI for malignancy of positive (class IV) cytology tests.

Predictive value of Patient group	Cytology class II (n = 14)	Cytology class III (n = 31)	Cytology class IV (n = 61)	Predictive value of cancer for class IV cytology (95% CI)
ATA- (n = 64)	Malignant: 0 (0%) Benign: 9 (100%)	Malignant: 6 (27.3%) Benign: 16 (72.7%)	Malignant: 27 (81.8%) Benign: 6 (18.2%)	81.8 (68.7–95.0)
ATA+ (n = 42)	Malignant: 0 (0%) Benign: 5 (100%)	Malignant: 0 (0%) Benign: 9 (100%)	Malignant: 27 (96.4%) Benign: 1 (3.6%)	96.4 (89.6–100)
Total (n = 106)	Malignant: 0 (0%) Benign: 14 (100%)	Malignant: 6 (19.4%) Benign: 25 (80.6%)	Malignant: 54 (88.5%) Benign: 7 (11.5%)	88.5 (80.5–96.5)

Table 3 Comparison of histological results found in 31 ATA+ and ATA- thyroid nodules with indeterminate (class III) cytology from patients who underwent surgery.

Histology	ATA-	ATA+
Benign (<i>n</i> = 25)	Follicular adenoma (<i>n</i> = 9) Nodular goiter (<i>n</i> = 7)	Hyperplastic nodule in lymphocytic thyroiditis (<i>n</i> = 6) Follicular adenoma in lymphocytic thyroiditis (<i>n</i> = 3)
Malignant (<i>n</i> = 6)	Follicular carcinoma (<i>n</i> = 5) Papillary carcinoma* (<i>n</i> = 1)	— —

*Follicular variant.

nodules associated with ATA +. This assumption is in apparent contrast with the histological results found in the subset of 106 patients that underwent thyroidectomy, since the prevalence of thyroid carcinomas in ATA + nodules was only marginally and not significantly higher (64.3%) than that found in ATA - nodules (51.6%). It should be noted, however, that since thyroidectomy was not indicated in the large majority of patients with benign (class II) cytology for obvious ethical reasons, it is conceivable that the final distribution of malignant vs benign lesions does not represent the initial distribution in all consecutive studied nodules, due to the selection process for surgery being dictated by cytological and other (echographic, scintigraphic, clinical) criteria. Indeed, when all the patients who underwent FNAC were considered, the number of cancers found in ATA + nodules was significantly higher than that found in ATA - nodules. Admittedly, an important but unavoidable limitation of the present study is represented by the impossibility of calculating a reliable predictive value for negative (class II) cytology tests, due to the very small number of class II nodules that received surgery. An interesting and somewhat surprising finding was that no thyroid cancer was found in class III ATA + nodules compared with the about one-third malignancies found in ATA - nodules in the same cytological class. Although the low number of class III nodules subject to thyroidectomy prevents an accurate statistical analysis, it would appear that in some cases autoimmune thyroiditis might be responsible for minor cytological abnormalities of follicular cells unrelated to neoplastic lesions. Comparison of the histological results of the operated class III ATA + and ATA - nodules provided some insights to explain this finding. While, as expected, the majority of class III ATA - nodules were follicular neoplasms (of which one-third were malignant), atypical follicular hyperplasia in a background of lymphocytic thyroiditis was the prevalent lesion found in ATA + nodules. These atypias appear to be mostly non-specific, since accurate cytological revision of all operated class III nodules failed to identify peculiar features in ATA +, when compared with ATA - patients. A wide spectrum of peculiar cytological and histological abnormalities has been described in a large surgical series of hypothyroid, euthyroid and hyperthyroid HT, with important correlations with the functional thyroid

status (19). The relevance of these observations for our study, which included only euthyroid patients, is difficult to establish.

Another interesting finding of our study was that PTC was the most prevalent form of thyroid tumor in ATA + patients, a finding in keeping with several previous retrospective pathological studies (5, 8, 20) reporting a specific association between HT and PTC rather than other thyroid tumor histotypes. Further support for an association between HT and PTC has been provided by recent studies reporting the finding in HT glands of immunohistochemical markers of PTC such as cytokeratin 19 (21) and p63 (22) and RET/PTC rearrangements (23–26), although the latter finding has not been confirmed (27). Due to the relatively small number of operations performed so far, we did not carry out a complete histological study in order to compare circulating ATA titers with the precise pattern of lymphocytic infiltration in the operated glands and its relation to the benign or malignant follicular lesions. A detailed pathological examination is currently in progress, waiting for a larger number of operated patients.

In conclusion, our study performed on unselected, consecutive thyroid FNACs devoid of selection biases, showed that the presence of positive serum ATA not only did not exclude malignancy in single thyroid nodules, but also conferred an increased risk for suspect or clearly malignant FNACs, which was independent of other confounding factors such as age and sex. Comparison of positive predictive values of suspect cytology for thyroid cancer did not show any difference between ATA + and ATA- thyroid nodules, providing indirect evidence for a significant association between thyroid cancer (mostly papillary) and thyroid autoimmunity. On the other hand, mild cytological atypias unrelated to thyroid cancer may be responsible for some excess of undetermined cytological features in ATA + nodules.

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