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ORIGINAL ARTICLE

Diagnostic value of antithyroid peroxidase antibody for incidental autoimmune thyroiditis based on histopathologic results

Myung Ho Rho · Dong Wook Kim · Hyun Pyo Hong · Young Mi Park · Min Jeong Kwon · Soo Jin Jung · Young Wook Kim · Taewoo Kang

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Abstract Detection of antithyroid peroxidase antibody (TPOAb) is widely used in the diagnosis of autoimmune thyroiditis (AIT), but no research has evaluated the diagnostic accuracy of TPOAb detection using histopathologic reference standards. To fill this research gap, this study assessed the diagnostic accuracy of detection of TPOAb and that of other serological markers in asymptomatic patients who had been diagnosed with AIT by histopathologic analysis after thyroid surgery. After review of patient records, 598 patients who had undergone thyroid nodule surgery were enrolled for examination for thyroid parenchyma by a pathologist and classification into no co-existing lymphocytic thyroiditis, Hashimoto thyroiditis, or non-Hashimoto type of lymphocytic thyroiditis (NHLT). The correlation between patient serological data and thyroid parenchyma pathology was analyzed. Statistically significant differences ($P < 0.05$) were found between co-existing lymphocytic thyroiditis and no co-existing lymphocytic thyroiditis groups regarding thyroid-stimulating hormone (TSH) and TPOAb levels. And, TPOAb titer was significantly associated with the degree of inflammation. An abnormal TPOAb titer was found in 86 of the 598 patients (14.4 %) and the specificity of TPOAb detection for AIT diagnosis was found to be 96.9 %. The prevalence of Hashimoto thyroiditis and NHLT in the 560 papillary thyroid cancer (PTC) patients was found to be 7.9 and 17.9 %, respectively. The results indicate that TPOAb titer is associated with the degree of thyroid inflammation and that detection of TPOAb is a very specific means of diagnosing AIT. The results also indicate that the incidence of AIT and PTC coexistence is relatively high.

Keywords Antithyroid peroxidase antibody · Autoimmune thyroiditis · Hashimoto thyroiditis · Lymphocytic thyroiditis · Papillary thyroid carcinoma

M. H. Rho · H. P. Hong
Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108, Pyung-Dong, Jongro-ku, Seoul 110-746, South Korea

D. W. Kim (✉) · Y. M. Park
Department of Radiology, Busan Paik Hospital, Inje University College of Medicine, 633-165, Gaegeum-dong, Busanjin-gu, Busan 614-734, South Korea
e-mail: dwultra@lycos.co.kr

M. J. Kwon
Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea

S. J. Jung
Department of Pathology, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea

Y. W. Kim
Department of Occupational and Environmental Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Gyeongnam, South Korea

T. Kang
Department of Surgery (Busan Cancer Center), Pusan National University Hospital, Pusan National University College of Medicine, Busan, South Korea

Introduction

Autoimmune thyroiditis (AIT) is a slowly developing persistent inflammation of the thyroid that frequently leads to hypothyroidism and decreased function of the thyroid gland. Middle-aged women are most commonly affected by AIT. In addition to overt thyroiditis, roughly 10 % of the population presents with anti-thyroglobulin and anti-thyroid peroxidase antibody (TPOAb) test results [1–4] in

the apparent absence of thyroid disease by physical examination. Whether the detection of low levels of TPOAb in healthy individuals and/or patients with non-thyroid autoimmune diseases reflects normal physiology or an assay specificity problem, or whether it is a prodrome of autoimmune thyroid disease remains unclear.

While for many years AIT was thought to be uncommon, it is now recognized as one of the most common thyroid disorders. Such recognition may reflect changes in diagnostic modalities. Whereas, diagnosis of AIT had traditionally been made only by the surgeon at the time of surgery or by the pathologist after thyroidectomy, the increasing use of antibody-based serological tests has led to a significant increase in the frequent recognition and diagnosis of AIT. There is also reason to believe that incidence of AIT may be increasing.

Detection of AIT has been made on the basis of both clinical and laboratory findings. The Japanese guidelines for diagnosis of Hashimoto thyroiditis include diffuse swelling of the thyroid gland not due to any other condition (such as Graves' disease) and at least 1 of following laboratory findings: (a) a positive assay for anti-thyroid microsomal antibody or anti-thyroid peroxidase antibody (TPOAb), (b) a positive assay for anti-thyroglobulin antibody, and/or (c) detection of lymphocytic infiltration in the thyroid gland confirmed by cytologic examination [5]. Many patients are asymptomatic and/or present with only subclinical hypothyroidism. Detection of TPOAb, typically the first abnormality to appear during the development of hypothyroidism secondary to Hashimoto thyroiditis, is the most sensitive test for detecting AIT [6, 7].

To the best of the authors' knowledge, many cytomorphological and sonomorphological studies of AIT and its serological correlations have been performed [8–19], but no correlations between TPOAb and histopathologically diagnosed incidental AIT have been reported. South Korea is an iodine sufficient country [20] and is endemic for thyroid disease [21]. To fill this research gap, this study evaluated the results of immunoassay for detection of TPOAb and of measurement of other serological markers and the relationship between papillary thyroid carcinoma (PTC) and AIT in asymptomatic AIT patients who had been diagnosed by histopathologic analysis after thyroid surgery.

Materials and methods

Patients

Approval for this study was granted by the relevant institutional review board before subject selection began. The clinical and histopathologic data of patients who had undergone total, near-total thyroidectomy, or hemithyroidectomy for the treatment of nodular thyroid pathology at our hospital between January 2008 and December 2010, were collected for review. After patients with the exclusion criteria of clinical hyperthyroidism or hypothyroidism; non-thyroid autoimmune diseases, such as type I diabetes and pernicious anemia; post-partum thyroiditis; and autoimmune complications from treatment with therapeutic agents (i.e., amiodarone, interferon-alpha, lithium) were excluded, 599 patients (83 males and 416 females) remained in the sample. All the patients, whose age ranged from 19 to 75 years (mean 46 $\pm$ 10.5 years), had presented with nodular and mass-like lesion in the thyroid gland and undergone aspiration cytology before surgery. The final histopathologic diagnoses after surgery included PTC ($n = 560$), follicular thyroid carcinoma ($n = 4$), medullary thyroid carcinoma ($n = 4$), follicular adenoma ($n = 6$), nodular hyperplasia ($n = 23$), and nodular thyroiditis ($n = 2$).

In addition to their classification by main pathology, thyroid parenchyma adjacent to the thyroid nodule was classified into 1 of 3 groups by a pathologist (S.J.J) by retrospective re-examination of histopathologic slides: no co-existing lymphocytic thyroiditis, Hashimoto thyroiditis, or non-Hashimoto type of lymphocytic thyroiditis (NHLT). Patients presenting with the histopathologic criteria of progressive loss of thyroid follicular cells, a concomitant replacement of the gland by lymphocytes and the formation of germinal centers associated with fibrosis were diagnosed as Hashimoto thyroiditis. Patients presenting with diffuse infiltration of the thyroid gland with lymphocytes and other inflammation-related cells, but with none of the typical histopathologic criteria for diagnosis of Hashimoto thyroiditis, such as oxyphilic metaplasia, follicular atrophy, or follicular disruption, were diagnosed as NHLT. Patients presenting with none of Hashimoto thyroiditis or the other type of lymphocytic thyroiditis were diagnosed as no co-existing lymphocytic thyroiditis. Among 599 patients, 450 were diagnosed with no co-existing lymphocytic thyroiditis, 45 with Hashimoto thyroiditis, and 103 with NHLT. One patient was found to have underlying Grave's disease and was excluded from further evaluation.

Serological evaluation (measurement of T3, T4, thyroid-stimulating hormone [TSH], and TPOAb levels) of all patients was performed within the week before surgery. Electrochemiluminescent immunoassay using the Elecsys automatic system (Roche, Mannheim, Germany) was used for measurement of TPOAb titer with a serum TPOAb titer greater than 34 IU/mL considered abnormal.

Statistical analysis

Analysis of variance (ANOVA) test and Student's t-test were performed to examine the mean differences of

continuous variables (T3, T4, TSH, and TPOAb) among the three groups (no co-existing lymphocytic thyroiditis, Hashimoto thyroiditis, and NHLT) and between two groups (no co-existing lymphocytic thyroiditis and co-existing lymphocytic thyroiditis), respectively. Chi-square test was performed to examine the mean differences between the TPOAb titers of the male and female patients, and Pearson's correlation analysis was used to examine the relationships between age and TPOAb titer. We calculated the sensitivity (true positive/[true positive + false negative]), specificity (true negative/[true negative + false positive]), positive predictive value (true positive/[true positive + false positive]), negative predictive value (true negative/[true negative + false negative]), and accuracy ([true positive + true negative]/total) of the TPOAb titer for AIT diagnosis on the basis of histopathology results.

All data were analyzed by a statistical software package (SPSS for Windows version 12.0), and P value < 0.05 was considered an indication of statistical significance for all results.

Results

The results of the analysis of the serological data of the 3 patient groups are summarized in Table 1. Statistically significant differences were found between co-existing lymphocytic thyroiditis and no co-existing lymphocytic thyroiditis groups ($P = 0.018$ and $P < 0.0001$, respectively) and among the three groups ($P < 0.0001$) regarding TSH and TPOAb levels. However, no statistically significant differences were found between Hashimoto thyroiditis and NHLT groups regarding TSH level ($P = 0.954$), and no significant differences were found among the three groups regarding T3 and T4 levels ($P = 0.058$ and $P = 0.060$, respectively). And, TPOAb titer was correlated among the three groups and associated with the degree of inflammation (Fig. 1).

The incidence of abnormal TPOAb titer among the 598 patients was found to be 14.4 % (86/598), with the incidence among male patients found to be 9.6 % (8/83) and female patients to be 14.8 % (76/515). Neither the sex ($P = 0.199$) nor the age ($P = 0.715$) of the patients was found to be significantly related to TPOAb titer. Whereas, only 14 (3.1 %) of the 450 patients with no co-existing lymphocytic thyroiditis were found to have an abnormal TPOAb titer, 26 (57.7 %) of the 45 patients with Hashimoto thyroiditis and 46 (44.7 %) of the 103 patients with NHLT were found to have an abnormal TPOAb titer ($P < 0.0001$).

The diagnostic values of TPOAb titer for the co-existing and no co-existing lymphocytic thyroiditis groups are listed in Table 2. The sensitivity, specificity, positive and negative predictive values, and accuracy of the TPOAb titer for AIT diagnosis were found to be 48.6 % (72/148), 96.9 % (436/450), 83.7 % (72/86), 85.2 % (436/512), and 85.0 % (508/598), respectively.

Among the 560 PTC patients, the prevalence of Hashimoto thyroiditis and NHLT was found to be 7.9 % (44/560) and 17.9 % (100/560), respectively. Although 25.7 % (144 patients) of the PTC patients were histopathologically diagnosed with co-existing AIT and PTC, only 15 % (84/560) were found to have an abnormal TPOAb titer.

Discussion

Only 3 principal thyroid autoantigens—TPO, thyroglobulin, and the TSH receptor—have been confirmed to play a role in detection of AIT. Although the involvement of other autoantigens, such as the sodium iodide symporter, has been described, the diagnostic role of these autoantigens in thyroid autoimmunity has not been established using histopathologic reference standards of the thyroid gland [22]. TPOAb, the most sensitive test for AIT currently available, is used to measure the level of TPO, a key enzyme in the

Table 1 Serologic data before thyroid surgery

Serologic items	No co-existing lymphocytic thyroiditis	Hashimoto thyroiditis	Non-Hashimoto type of lymphocytic thyroiditis	*P*-value
Triiodothyronine (ng/dL)	109.76 ± 19.22 (19.2–195.9)	102.39 ± 20.38 (20.4–170.1)	108.44 ± 22.14 (22.1–227.3)	0.058
Free thyroxine (ng/dL)	1.29 ± 0.38 (0.27–8.09)	1.18 ± 0.34 (0.34–2.67)	1.26 ± 0.33 (0.18–3.11)	0.060
Thyrotropin (mIU/L)	1.92 ± 1.64 (0.005–20.51)	4.23 ± 11.59 (0.006–79.28)	4.36 ± 12.43 (0.005–100)	<0.0001
TPOAb (IU/mL)	11.39 ± 16.12 (0.32–207.5)	212.54 ± 276.93 (1.7–1000)	108.45 ± 164.81 (1.5–600)	<0.0001

Note: values are mean ± standard deviation with range in parentheses. TPOAb, antithyroid peroxidase antibody. *P* values of significant difference between three groups, by ANOVA test with statistical significance set at $\alpha = 0.05$

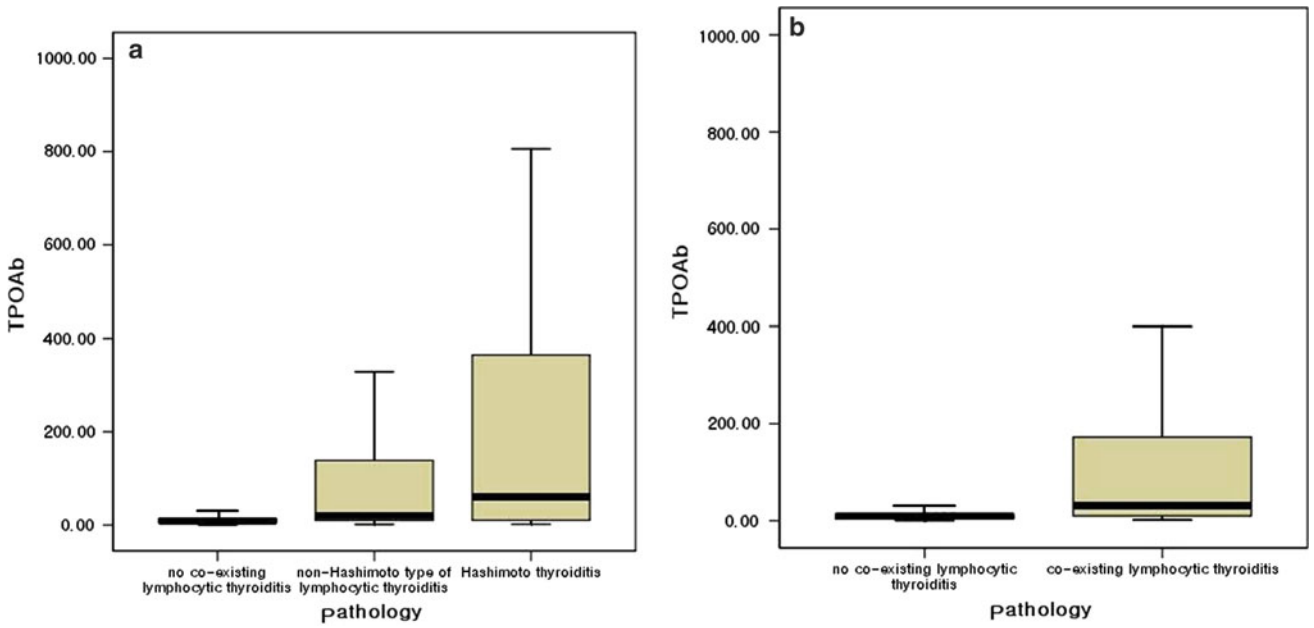

Fig. 1 Box plots of TPOAb titers for all 598 patients according to three (**a**) and two (**b**) groups classification

Table 2 The results of TPOAb titer in detection of incidental autoimmune thyroiditis (598 patients)

TPOAb level	No co-existing lymphocytic thyroiditis	Autoimmue thyroiditis	Total
Normal	436 (true negative)	76 (false negative)	512 (85.6 %)
Abnormal	14 (false positive)	72 (true positive)	86 (14.4 %)
Total	450 (75.3 %)	148 (24.7 %)	598

formation of thyroid hormones at the apical pole of the follicular cell and a major autoantigen in AIT [23]. Although a detectable TPOAb titer precedes the development of elevated TSH level (subclinical hypothyroidism) and low T4 level (overt hypothyroidism), a TPOAb titer is detected in some euthyroid patients (prevalence 12–26 %) [7, 17, 24]. Estimates of the prevalence of TPOAb detection depend on the sensitivity and specificity of the method employed. The National Health and Nutrition Examination Survey (NHANES) III, a survey of approximately ~17,000 subjects in the US without apparent thyroid disease, reported detectable TPOAb levels in 12 % of subjects using a competitive immunoassay method [25]. In the present study, 14.4 % of patients were found to have an abnormal TPOAb titer that was not associated with PTC or other tumorous conditions, a prevalence similar to that of the general population.

A cytomorphological study of Hashimoto thyroiditis and its serological correlations indicated that the grading of thyroiditis and lymphocytic infiltration is not correlated with the clinical severity of Hashimoto thyroiditis, but that a high lymphoid-to-epithelial (L:E) ratio is strongly correlated with TPO positivity ($P = 0.004$) [7]. When the AIT cases in this study were divided into Hashimoto thyroiditis and NHLT cases by histopathologic criteria that identified Hashimoto thyroiditis as a more severe form of AIT rather than of NHLT, TPOAb titer was found to be correlated with the degree of thyroid architecture destruction, as well as with the degree of thyroiditis.

Since first being proposed in 1995 [26], the identification of AIT as a predisposing factor for PTC has been controversial. Matsubayashi et al. [27] reported that lymphocytic infiltration surrounding or inside the tumor in PTC patients is the result of immune responses, and thus might be a marker predicting favorable prognosis, and suggested that high-grade PTC with no lymphocytic infiltration is likely to recur. Cipolla et al. [28] suggested that AIT and PTC coexist in several morphological, immunohistochemical, and biomolecular aspects, increased incidence of PTC in AIT patients might indicate that AIT is a precursor of thyroid cancer. However, in a study of a large series of patients, the incidence of AIT and PTC coexistence in cytologic material was found to be only 0.4%, and no significant relationship was found between AIT and PTC in the cytologic material [29]. Mazokopakis et al. [30] found the prevalence of AIT and PTC coexistence in the histopathologic material of 140 thyroidectomized patients to be 8.6 %. In this study, the incidence of coexisting AIT with PTC was found to be 25.7 %, and incidence similar to that found by Cipolla (26.7 %), but higher than that found by other studies [29, 30]. These discrepant findings call for

further research to confirm the hypothesis that AIT is a predisposing factor for PTC. However, the incidence of abnormal TPOAb levels in PTC patients and the incidence of detectable TPOAb levels in patients with no co-existing AIT were found to be similar in this study. Recently, Moon et al. [31] reported that if the thyroid nodules of lymphocytic thyroiditis patients observed to have suspicious malignant features on sonography show no change or an increase in size on follow-up examination, follow-up sonography-guided fine-needle aspiration should be performed.

As all the patients in this study had tumorous conditions and most had PTC, the results obtained by their examination cannot be generalized to the general adult population. Moreover, because surgery had been performed independently and regardless of TPOAb level, as well as because of the limits faced in patient selection, this study was unable to determine whether subclinical hypothyroidism in patients with high TPOAb titers tends to develop into overt hypothyroidism. To address this consideration, clinical and serological follow-up of large samples of hemithyroidectomy patients with high TPOAb titers should be conducted to determine whether there is a causal relationship between a high TPOAb titer and the development of overt hypothyroidism. In addition, a quantitative analysis of the lymphocyte infiltration, such as by measuring the number of CD45-positive cells and correlating this with the TPOAb titer, was not performed in this study. Therefore, further quantitative analysis on the basis of examination of histopathologic specimens and correlated biomarkers may be required.

In conclusion, this study found that TPOAb titer is associated with the degree of thyroid inflammation and that detection of TPOAb titer is a very specific means of diagnosing incidental AIT. In addition, a high incidence of incidental AIT and PTC coexistence was observed among the study subjects.

Disclosure No competing financial interests exist.

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