Antithyroid peroxidase antibody positivity is associated with lower incidence of metastasis in breast cancer

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Abstract. Thyroid extracts were first used to treat patients with metastatic breast cancer over a century ago. Since then, a number of studies have investigated the association between thyroid disorders and breast cancer. The presence of antibodies to thyroid peroxidase (TPOab) was recently reported to be associated with improved outcome in these patients. The aim of the present study was to evaluate the association between TPOab positivity and clinicopathological characteristics in breast cancer patients. The study included 318 newly diagnosed cases of breast cancer treated at Ondokuz Mayis University Hospital, Samsun, Turkey, between 2008 and 2012. Serum thyroid-stimulating hormone, free triiodothyronine and free thyroxine levels were measured at the time of diagnosis. Of the 318 patients, 253 were considered to be TPOab-negative (TPOab ≤34 IU/ml) and 65 TPOab-positive (TPOab >34 IU/ml). No cases with distant metastases were found in the TPOab-positive group. However, 20 (7.9%) of the 253 patients displayed distant metastases in the TPOab-negative group (P=0.01). Therefore, TPOab positivity was found to be associated with a lower incidence of metastasis in breast cancer patients.

Introduction

Since Beatson (1) first described the use of thyroid extracts to treat patients with metastatic breast cancer over a century ago, a number of studies have investigated the association between thyroid disorders and breast cancer (2-8). However, despite extensive population studies, the results as a whole have been inconsistent. In preclinical models, it has been found that T3 may sustain serum-free proliferation of several cell lines, including breast cancer; in addition, rodent mammary gland development and physiology have been found to be sensitive to T3 (9-11).

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Recent reports have refocused attention on the long-debated question of the possible assosiation between autoimmune thyroid disease (AITD) and breast cancer; some of the studies reported a positive association (3,12), but this was not confirmed in other studies (6).

Thyroid peroxidase (TPO), is one of the main known autoantigenic targets in the thyroid gland, similar to thyroglobulin or nuclear thyroid hormone receptor, and is the antigen most closely involved in cell-mediated cytotoxicity (13-15). An elevated level of antibodies to TPO (TPOab) was reported to be the major risk factor for AITD (16). With sensitive assay techniques, 95% of the patients with hypothyroidism (Hashimoto's thyroiditis) and 85% of those with hyperthyroidism (Graves' disease) have detectable levels of TPOab (17).

It was previously reported that the AITD prevalence is higher among breast cancer patients compared to that among healthy subjects (18-20). Surprisingly, Smyth (21) demonstrated that TPOab level is inversely correlated with tumor size and axillary nodal involvement and significantly improves the outcome of breast cancer patients.

The objective of the present study was to investigate the association between TPOab and the clinicopathological characteristics of breast cancer patients.

Patients and methods

Patients. A total of 318 female newly diagnosed breast cancer patients, who were diagnosed and treated at the Ondokuz Mayis University Hospital, Samsun, Turkey, between 2008 and 2012, were included in our study. Patients with previous cancer history and those who had received therapy for thyroid disease were excluded.

Following provision of written informed consent, all the patients underwent a staging workup according to the National Comprehensive Cancer Network guidelines (https://intervalolibre.files.wordpress.com/2012/06/mama-2014.pdf).

Prior to treatment initiation, baseline serum samples were obtained to measure TPOab, serum free triiodothyronine (fT3), free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels.

The study protocol was approved by the Ethics Committee of Ondokuz Mayis University and conformed to the standards of the Helsinki Declaration.

Table I. Characteristics of TPOab-positive and -negative patients (n=318).

Characteristics	TPOab ≤ 34 IU/ml, no. (%) (n=253)	TPOab > 34 IU/ml, no. (%) (n=65)	P-value
Age, years	49.9±9.9	50.2±8.7	0.850
fT3, pg/ml	3.06±0.53	3.06±0.54	0.999
fT4, ng/dl	1.18±0.302	1.17±0.25	0.120
TSH, μIU/ml	2.81±2.89	4.48±4.9	**0.000**
Nuclear grade			0.549
I	30 (11.9)	11 (16.9)	
II	163 (64.4)	39 (60.0)	
III	60 (23.7)	15 (23.1)	
Tumor size, cm			0.800
T1, ≤2	93 (36.8)	25 (38.5)	
T2-4, >2	160 (63.2)	40 (61.5)	
Lymph node metastasis			0.575
Negative	107 (42.3)	30 (46.2)	
Positive	146 (57.7)	35 (53.8)	
Metastasis			0.018
M0	233 (92.1)	65 (100.0)	
M1	20 (7.9)	0 0.0)	
Estrogen receptor			0.128
Positive	191 (75.5)	43 (66.2)	
Negative	62 (24.5)	22 (33.8)	
Progesterone receptor			0.147
Positive	146 (57.7)	31 (47.7)	
Negative	107 (42.3)	34 (52.3)	
HER2/neu			0.385
Positive	181 (71.5)	50 (76.9)	
Negative	72 (28.5)	15 (23.1)	
Local recurrence-distant metastasis			0.040
Negative	239 (88.5)	64 (96.9)	
Positive	14 (11.5)	1 (3.1)	

The values are presented as mean ± standard deviation. Bold print denotes statistically significant differences. TPOab, antibodies to thyroid peroxidase; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; HER2, human epidermal growth factor receptor 2.

TPOab and hormone detection. TPOab, TSH, fT3 and fT4 levels were quantitatively measured using electrochemiluminescence immunoassay kit (Modular Analytics Evo e170; Roche Hitachi Corp., Tokyo, Japan). Normal ranges were defined according to the laboratory kits used as follows: TPOab, 0-34 IU/ml, with the cut-off level set at 34 IU/ml (all cases with TPOab ≤34 IU/ml were considered to be negative, whereas all cases with TPOab >34 IU/ml were considered to be positive.

Pathological evaluation. The following characteristics were investigated in all patients following breast surgery: Nuclear grade, estrogen receptor (ER) and progesterone receptor (PgR) expression, tumor size, lymph node metastasis and human epidermal growth factor receptor 2 (HER2)/neu status.

ER and PgR status and HER2 overexpression were determined by standard immunohistochemical analyses. In case of uncertainty, fluorescence *in situ* hybridization was performed.

Statistical analysis. Statistical analyses were performed using SPSS software for Windows, version 15 (SPSS, Inc., Chicago, IL, USA) and the results are expressed as mean ± standard deviation. In all the tests, the $P<0.05$ was considered to indicate a statistically significant difference.

The differences in categorical variables (nuclear grade, pTNM status and hormone receptor status) between the TPOab-positive and -negative groups were analyzed with the Pearson's χ^2 test. The Mann-Whitney U test was used to evaluate the differences in TSH, fT3 and fT4 between the two groups.

Results

Patients. Of the 318 newly diagnosed patients with breast cancer, 253 patients (79.6%) with TPOab levels ≤34 IU/ml were considered as TPOab-negative and 65 (20.4%) with TPOab >34 IU/ml as TPOab-positive. All the metastases were detected at the time of diagnosis. No cases with distant metastases were identified among the 64 patients in the TPOab-positive group. However, 20 (7.9%) of the 253 TPOab-negative patients displayed distant metastases (P=0.018) (Table I).

Differences in patient characteristics according to TPOab levels. There were no significant differences between the TPOab-negative and -positive patient groups with respect to age (P=0.850), fT3 (P=0.999) and fT4 (P=0.120), nuclear grade (P=0.549), tumor diameter (P=0.800), lymph node involvement (P=0.575), ER status (P=0.128), PgR status (P=0.147) and HER2/neu status (P=0.385) (Table I).

However, TPOab-positive patients exhibited higher TSH levels compared to TPOab-negative patients (2.81 vs. 4.48 μIU/ml, respectively; P=0.000).

Although all the patients could not be followed up over the same time period, in the TPOab-positive group only 1 patient developed distant metastasis, whereas in TPOab-negative group, distant metastasis or local 0recurrence was identified in 14 patients (P=0.040).

Discussion

Since the 1950s, over 30 studies have been published on the association between thyroid disorders and breast cancer; however, this association remains controversial (2-8). In 2002, Sarlis *et al* (22) and Simon *et al* (23) reported no association between breast cancer and thyroid disorders; however, Cristofallini *et al* (24) later demonstrated that patients with primary hypothyroidism exhibited a reduced risk for developing invasive breast cancer and that patients with invasive breast cancer and hypothyroidism may have a more indolent disease course, as they were significantly more likely to have pathologically smaller tumors. The data also suggested that lymph node involvement and hormone receptor-negative tumors (e.g., ER-negative) were also less frequent among hypothyroid patients, but this association was not statistically significant. In agreement with our study, Farahati *et al* (25) recently reported that the presence of TPOab is associated with a lower frequency of metastasis in breast cancer patients. However, in addition to that study, we observed that TPOab positivity may protect breast cancer patients from local recurrence or distant metastasis during the follow-up period. Similar to our findings, Smyth (21) reported a better disease outcome in 142 breast cancer patients with elevated TPOab levels compared to TPOab-negative cases. However, we were unable to identify any association between nuclear grade, ER, PgR and HER2/neu status, lymph node involvement and TPOab positivity. In March, 2014 a study conducted in Italy demonstrated that breast cancer prevalence is higher among patients with thyroid diseases; however, the subgroup analysis demonstrated that TPOab and/or antithyroglobulin antibody positivity appear to be protective against breast cancer (26).

The mechanisms through which TPOab positivity may affect breast cancer progression have not been fully elucidated. TPOab positivity has been shown to be an important factor in antibody-dependent cell cytotoxicity in the thyroid gland (27) and there may be an association between autoimmune thyroiditis and protective antitumor mechanisms. Therefore, high TPOab levels may represent an immune response against breast carcinoma and/or thyroid tissue (15,21).

Thyroid hormones are involved in mammary gland development by stimulating ductal branching and alveolar budding (11). Normal mammary epithelial cells express significant amounts of thyroid hormone receptor - a member of nuclear receptor family (28,29) and breast cancer cells exhibit T3-binding activity (30,31). Although little was known on this issue, several investigations recently suggested that TSH and T3 may stimulate proliferation in some experimental models (24).

Spitzweg *et al* (32) reported that breast cancer and thyroid tissue express sodium iodide symporter genes; and Kilbane *et al* (33) demonstrated that breast cancer tissue iodine content was significantly lower compared to that in normal breast tissue or fibroadenoma, suggesting an iodine uptake pathology in breast cancer. Previous epidemiological studies demonstrated an inverse correlation between iodine intake and breast cancer incidence (12,34).

Our study demonstrated that TPOab positivity is associated with a lower incidence of metastatic cases among breast cancer patients and a better outcome compared to negative cases.

In conclusion, primary hypothyroidism and AITD, particularly TPOab positivity, may be good prognostic factors in breast cancer patients; however, further investigations are required.

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