

The Relationship Between Lymphocytic Infiltration in the Thyroid Gland and Tumor Recurrence in Papillary Thyroid Carcinoma

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The purpose of this study was to determine whether lymphocytic infiltration surrounding and/or inside the tumor would predict a favorable prognosis in patients with papillary thyroid carcinoma (PTC). The data obtained from twenty-five patients of PTC with both classic (n=15) and microcarcinoma (n=10) subtypes who were followed up for an average of 6.6 years (5 to 10 years) were evaluated retrospectively. The patients were subdivided according to whether or not there was lymphocytic infiltration in the thyroid gland. Group A consisted of 12 patients with lymphocytic infiltration whereas group B consisted of 13 patients with no lymphocytic infiltration.

There were no differences in age, sex, initial tumor size, type of initial treatment, or antithyroid antibody frequencies between the two groups. None of the patients in group A had recurrence of tumor, but three patients in group B had recurrence. The duration between initial treatment and recurrence in these patients was 3, 4 and 6 years, respectively. In relation to the clinical class at the time of initial treatment, recurrence was detected in one case in each of classes I, II and III. Recurrence was detected in only one patient whose tumor size was less than 1cm (microcarcinoma) whereas 2 others who had primary tumor size ranging from 1 to 3 cm (classic subtype) recurred. All patients were alive and tumor free at their last visit. Our preliminary results suggest that lymphocytic infiltration of the thyroid gland in PTC seems to be a favorable prognostic marker. But, further studies of larger groups of patients are necessary to determine the role of lymphocytic infiltration in the prognosis of PTC.

KEY WORDS Papillary thyroid carcinoma, lymphocytic infiltration, histologic subtypes, prognosis

Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid carcinoma, comprising about 80% of all thyroid tumors (1-3). Major factors contributing to disease outcome are patient's age at the time of diagnosis, tumor size,

multifocality, direct extrathyroidal tumor invasion, cervical lymph node involvement, distant metastases, delay in early detection, use of more extensive initial surgery in tumors more than 1cm in size, and postoperative radioactive ¹³¹I ablation of thyroid remnant tissue (4-8). Because growth patterns and tumor behavior of papillary cancer vary widely with regard to histologic subtype, classifying the tumor into distinct pathologic subgroups is also important (1-3). Although lymphocytic infiltration is frequently observed in PTC (9-13), only a few studies have evaluated lymphocytic infiltration within the thyroid gland and its

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association with the prognosis of PTC (14). The authors found that lymphocytic infiltration surrounding or inside the tumor in PTC might be useful in predicting a favorable prognosis. It is known that histologic subtype of PTC also affects the prognosis of the disease (1-3). However, this was not taken into account in previous studies (14,18). We investigated the relationship between tumor recurrence and lymphocytic infiltration surrounding or inside the primary tumor in patients with classic and microcarcinoma variants of PTC.

Subjects and Methods

We have analyzed the data obtained from 25 patients with classic (usual) or microcarcinoma subtype of PTC who were followed up for an average of 6.6 years and whose pathological diagnoses were made in our institution. The clinical approach in these patients in our institution is total or near total thyroidectomy followed by an empirically determined dose of ^{131}I treatment in order to ablate post-surgical residual thyroid tissue and/or treat other disease. Patients were treated with sequential doses of ^{131}I at intervals of 6-12 months until ^{131}I uptake was absent. Suppressive therapy with thyroid hormone, usually LT_4 , in an amount adequate to suppress TSH to a low normal level was also given.

The study group consisted of 25 patients, 20 females and 5 males. Duration of follow-up was median 6.6 years (5 to 10 years). At their last follow-up, all patients were alive and free of disease.

Patients were classified for the extent of disease at the time of diagnosis according to DeGroot's classification (4). Class I included patients with intrathyroidal disease. Class II included patients with positive cervical nodes. Class III included patients with extrathyroidal neck invasive disease, which was believed not to be totally resected. Class IV patients had distant metastases.

The patients were subdivided according to whether or not there was a lymphocytic infiltration in the thyroid gland. The patients who were operated on

and followed-up in our institution were included in this study. The patients were retrospectively analyzed and classification was performed without knowing the clinical outcome by a pathologist. Group A consisted of 12 patients with PTC associated with lymphocytic infiltration whereas group B consisted of 13 patients with no lymphocytic infiltration. Group A tumors demonstrated a moderate to marked lymphocytic infiltration, and rarely the presence of germinal centers. This change was more pronounced at the tumor periphery and within the fibrovascular papillary stalks. Group B tumors demonstrated no lymphocytic infiltration, or scattered lymphocytes at the tumor periphery.

The type of surgical treatment for group A was total or near total thyroidectomy (TT) for 11 patients and TT with modified neck dissection for 1 patient. In group B all patients underwent TT or near total thyroidectomy. All patients received postoperative radioactive ^{131}I ablation. Cancer recurrence was classified as new evidence of disease occurring more than 12 months after diagnosis. The patients were systematically studied for recurrence and the presence of cancer was established by radioiodine scans, thyroglobulin assessment, x-rays or clinical examination.

The statistical analyses used were Student's t test with a Bonferroni correction for comparison of parametric values between groups and Fisher exact test for comparison of frequency between groups.

Results

A comparisons of clinical characteristics between patients with PTC associated with (group A) or without lymphocytic infiltration (group B) in the thyroid gland is shown in Table 1. No differences were found in age, sex, tumor size, lymph node metastasis, multifocality, or tumor invasion into the contiguous neck structures between group A and B.

Ten patients from group A and 8 patients from group B were in class I ($P=0.22$). One patient from each group was in class II ($P=0.74$). One patient from group A and 4 patients from group B were in class III ($P=0.19$). The frequency of Class III is much higher in group B than in group A.

Table 1. Clinical characteristics of patients with papillary thyroid carcinoma with or without lymphocytic infiltration surrounding or inside the tumor.

	Lymphocytic infiltration		P Value
	Present (Group A; n:12)	Absent (Group B; n:13)	
Age (year)	48.7±15.4	46.5±14.2	NS
Sex (M:F)	2:10	3:10	NS
Tumor size (cm)	1.38±0.98	1.42±0.93	NS
Lymph node metastasis	1 (8.3 %)	1 (7.6 %)	NS
Multifocality	1 (8.3 %)	2 (15 %)	NS
Tumor invasion into neck structure	1 (8.3 %)	3 (23 %)	NS
Surgical treatment			
Total thyroidectomy	11	13	NS
TT+ MND	1	0	NS
ATA positive	2 (16.6 %)	2 (15 %)	NS
AMA positive	4 (33.3 %)	3 (23 %)	NS
Coexistence of thyroid disease			
Adenomatous goiter	4 (33.3 %)	5 (38.4 %)	NS
Chronic lymphocytic thyroiditis	6 (50 %)	0 (0 %)	NS
Histologic variants			
Classic (n)	7	8	NS
Microcarcinoma (n)	5	5	NS

Values are the mean ±SD. Percentages are given in the parenthesis. MND: modified neck dissection, ATA: antithyroglobulin antibody, AMA: anti-microsomal antibody

Table 2. Classification of clinical stage and primary tumor size at diagnosis and recurrence of the tumor during follow-up.

Lymphocytic infiltration in the thyroid gland							
		Present (n: 12)			Absent (n: 13)		P*
Tumor size (cm)	Class I	Class II	ClassIII	Class I	ClassII	ClassIII	
< 1	5	0	0	5 (1)	0	0	NS
1- 3	5	1	1	3	1 (1)	4 (1)	NS
Total	10	1	1	8 (1)	1 (1)	4 (1)	NS

Cases of recurrent tumor are given in parenthesis

*Comparison of recurrences between groups by Fisher exact test.

The frequency of positive antimicrosomal (AMA) (P=0.45) and/or antithyroglobulin (ATA) (P=0.67) antibodies was not significantly different between the two groups.

Coexisting thyroid disease such as adenomatous goiter was found in 4 patients from group A and 5 patients from group B (P=0.56).

Chronic lymphocytic thyroiditis was found in 6 patients from group A and no patient from group B (P<0.01). However, After Bonferroni correction, this significance was lost.

Three patients from group B had recurrence of tumor during follow-up, however no recurrence was found in group A (P=0.22) (Table 2). Of those, 2 were males and one was female. Ages of

these patients at the time of diagnosis were 48, 20 and 40 years, respectively. In group A, no patients had recurrence. The duration between initial treatment and recurrence was 3, 4 and 6 years, respectively. The recurrence was also evaluated according to primary tumor size in Table 2. Only one patient with PTC less than 1cm in size had recurrence, whereas 2 patients whose primary tumor size ranged from 1 to 3 cm had recurrence. On the basis of clinical stage at the time of initial treatment, recurrence was found in one patient in each of the classes I, II and III.

Discussion

The results of our preliminary study show that recurrent disease was only observed in patients

with no lymphocytic infiltration of papillary cancer. None of the patients with lymphocytic infiltration had recurrent disease compared with 3 of 13 (23.0 %) patients without an infiltrate. Although our findings do not reach statistical significance, probably due to the small number of the patients, these preliminary results support the view of Matsubayashi et al. (14) that patients with lymphocytic infiltration more commonly presented lower classes of disease at the time of resection and tumors were confined to the thyroid gland.

It is known that variants of papillary cancer such as tall-cell, columnar and diffuse sclerosing variants have been associated with poor prognosis (1-3). Thus, in our study, unlike Matsubayashi et al. (14), we evaluated only the outcome of patients with classic and microcarcinoma subtypes of PTC in order to prevent different effects of various subtypes of PTC on the prognosis. The reason why we selected these subgroups is that the biological behaviors of the classical and microcarcinoma variants of PTC demonstrates similar features (1-3). Thus, this is the first study for the evaluation of the relationship between lymphocytic infiltration and prognosis in histologic variants of PTC.

Frequency of positive antithyroid antibodies was also not significantly different between the two groups suggesting that they are not a marker sensitive enough to predict a better prognosis (15). Pacini et al. (16) also reported that the presence of circulating thyroid autoantibodies does not represent a protective or worsening factor in the history of thyroid cancer.

In previous studies, coexistence of diffuse lymphocytic thyroiditis and thyroid cancer has varied from 0.5-22.5 % (4,12,17). If focal thyroiditis is also considered, the ratio rises to 50% (11,12). It is of interest that several years ago, Meier et al. observed that patients with lymphocytic infiltration adjacent to the carcinoma had fewer nodal metastases than patients without focal thyroiditis (11). Hirabayashi and Lindsay (12) also reported that patients with thyroiditis and thyroid cancer have a better survival rate. Recently, Kashima et al (18) also reported that chronic thyroiditis is a favorable prognostic factor in PTC. Other researchers also reported frequent mononuclear cell infiltrates

in the papillary thyroid cancer (17). These studies suggested that there may be a relationship between PTC and autoimmune thyroid disease (AITD). However, Bagnasco et al. (19) reported that the functional repertoire of T cells is different in PTC and AITD, thus suggesting a different pathophysiological role of the immune system in the two diseases. Moreover, Aguayo et al. (10) concluded that PTC, unlike AITD, was not primarily related to immune system derangement and that the observed features of autoimmunity such as focal lymphocytic infiltration and DR expression on thyrocytes are local and secondary phenomena. However, it is of interest that observation of no recurrence in our patients with a lymphocytic infiltration surrounding or inside the tumor at resection suggests that the immune system may control the growth and spread of PTC, although the mechanism is not clear. It is possible that infiltrated lymphocytes may be cytotoxic T cells which destroy the neoplastic cells (19,20) or secrete cytokines that inhibit thyroid carcinoma cell growth and limit distant metastasis (21,22). Another possibility is that the tumor itself may produce soluble thyroid antigens or soluble MHC antigens that suppress the immune response to papillary cancer (15,23,24).

Our results support the view of Matsubayashi et al. (14) that any patient who lacks a lymphocytic infiltration surrounding and/or inside the tumor should be monitored carefully for recurrence of the tumor.

It should be noted that several years ago, immunotherapy for differentiated thyroid cancer was tried on patients with terminal thyroid cancer with transient clinical response by DeGroot's group (13). They suggested that the timing of active immunization was too late to induce or restore cell mediated immunity. Lo Gerfo et al. (25) also tried immunotherapy by induction of autoimmune thyroiditis in humans with untreatable metastatic cancer. In this study the clinical response to the immunotherapy was minimal. Thus future studies are necessary to determine the role of lymphocytic infiltration in the prognosis of PTC subtypes.

Overall, our preliminary results in a small group of patients suggest that lymphocytic infiltration of the

thyroid gland seems to be a favorable prognostic marker in PTC. Thus, further studies of larger groups of patients are necessary to determine the role of lymphocytic infiltration in the prognosis of PTC subtypes.

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