



Coexistence of Primary Mucosa-Associated Lymphoid Tissue Lymphoma of Thyroid and Papillary Thyroid Microcarcinoma in a Background of Hashimoto's Thyroiditis

Hashimoto Tiroiditi Zemininde Tiroidin Primer Mukoza İlişkili Lenfoması ve Papiller Mikrokarsinom Birlikteliği

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Abstract

Papillary thyroid carcinoma (PTC) is the most common endocrine cancer; however, extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) of the thyroid gland is quite rare. The comorbid condition of both cancers is an infrequent event. In the present study, we report a 65-year-old woman, who underwent a thyroid ultrasound examination due to palpable thyroid nodules. The reports of the thyroid ultrasound revealed thyroiditis and the presence of multiple nodules on both lobes. Although the results revealed that biopsies were benign, total thyroidectomy was performed due to the presence of multiple nodules that may become difficult for the subsequent follow-up. Histopathological analysis exhibited the presence of papillary thyroid microcarcinomas in two foci, Hashimoto's thyroiditis accompanied with MALT lymphoma. No metastasis was found in postoperative computed tomography scans. However, bone marrow biopsy indicated uniform marginal zone lymphoma. From the result, it can be concluded that PTC and primary thyroid lymphoma may be associated with Hashimoto's thyroiditis, and for both the diseases multimodal approach is required.

Keywords: Papillary thyroid carcinoma; lymphoma; Hashimoto's thyroiditis

Özet

Papiller tiroid karsinomu [papillary thyroid carcinoma (PTC)] en yaygın endokrin kanserdir; bununla birlikte tiroid bezinin mukoza ile ilişkili lenfoid dokusunun [mucosa-associated lymphoid tissue (MALT)] ektranodal marjinal zon lenfomasına nadir bir durumdur. Her 2 kanserin eşlik eden durumu nadir görülen bir durumdur. Bu çalışmada, ele gelen tiroid nodülleri nedeni ile tiroid ultrasonu yapılan 65 yaşındaki bir kadın olguyu sunduk. Tiroid ultrasonunda tiroidit ve her 2 lobda birden fazla nodül saptandı. Biyopsi sonuçları benign olmasına rağmen, nodül sayısının çok olmasına bağlı takip zorluğu nedeni ile total tiroidektomi yapıldı. Histopatolojik analiz, Hashimoto tiroiditi zemininde MALT lenfomaya eşlik eden 2 odakta papiller tiroid mikrokarsinomu varlığını gösterdi. Postoperatif bilgisayarlı tomografi taramalarında metastaz saptanmadı. Bununla birlikte, kemik iliği biyopsisinde marjinal zon lenfoma saptandı. Sonuç olarak, PTC ve primer tiroid lenfomasının Hashimoto tiroiditi ile ilişkili olabileceği ve her 2 hastalık için de multimodal yaklaşımın gerekli olduğu sonucuna varılabilir.

Anahtar kelimeler: Papiller tiroid karsinomu; lenfoma; Hashimoto tiroiditi

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Introduction

Thyroid cancer is the most common endocrine neoplasia. Between 2004 and 2013, the estimated incidence of thyroid carcinoma increased by an average of 5% annually. However, the incidence rate has been recently stabilized (1). Among all thyroid cancers, papillary thyroid cancer (PTC) accounted for 75-85% of all cases and occurs predominately in women with excellent prognosis (2). On the other hand, primary thyroid lymphoma is a rare condition, where only 2% of extranodal lymphomas develop in the thyroid gland. These lymphomas account for less than 2% of thyroid cancers (3). The co-occurrence of PTC and PTL is a rare condition. The purpose of this case report is to emphasize the incidence of primary thyroid lymphoma in adjunct with thyroid papillary carcinoma, which may have some association in people with a background of Hashimoto's thyroiditis.

Case Report

In September 2018, a 65-year-old woman underwent a thyroid ultrasound examination due to the presence of palpable nodules in the thyroid gland. Thyroid ultrasonography (USG) of the nodules exhibited being them solid, hypoechoic, having a well-defined margin. The largest of which was 2.5 cm in the right lobe and 2 cm in the left lobe. Fine needle aspiration biopsies revealed benign cytopathology for two nodules. However, the patient was advised to undergo surgery for having a considerable number of nodules, which may cause difficulty in subsequent follow-ups.

The outcomes of the routine laboratory tests were found to be well within the normal range. Estimation of serum hormone revealed the concentration of thyroid-stimulating hormone was 1.80 mU/L (reference range 0.27-4.2 mU/L), free thyroxine (T₄) was 0.85 ng/dL (reference range 0.58-1.6 ng/dL), thyroglobulin antibodies was 133 IU/mL (reference range 0-4 IU/mL) and peroxidase autoantibody was 1.3 IU/mL (reference range 0-9 IU/mL).

In November 2018, total thyroidectomy was performed on the patient, keeping the lymph nodes intact. Histopathological analysis revealed the presence of papillary thyroid microcarcinomas in the right lobe was

0.45 cm and in the left lobe was 0.6 cm in diameter. A predominant follicular pattern was observed in the left lobe (Figure 1A) accompanied with extranodal marginal zone lymphoma. The alterations were observed in diffuse large B-cell lymphoma (DLBCL) along with lymphoid cell infiltration, necrosis, and necrobiosis impairing the thyroid parenchyma. Most of the cells are of medium size and large notched cells were detected in layers at several foci. It was observed that the identified cells developed to form follicular epithelium in some foci and further formed lymphoepithelial a lesion or sometimes aggregates in the follicular. The identified cells were mostly CD20 positive with a small number of CD3+ T lymphocytes. Infiltration of CD5, CD23, cyclinD1, and CD43 was absent, whereas the presence of diffuse positive CD10 and bcl-6 was noted. Bcl2 staining in medium-sized cells showed 10% prevalence (Figure 1B), while Ki67 proliferative activity was above 90% (Figure 1C). Lymphoepithelial lesions and lymphoid balls were made observable after staining it with CK7, whereas C-myc was found negative.

No B symptoms related to lymphomas such as fever, weight loss or nocturnal sweating were absent in the patient. The staging procedures that included contrast-enhanced computed tomography of the neck, thorax/mediastinum, and abdomen revealed no evidence of metastasis, but bone marrow biopsy showed consistent marginal zone lymphoma metastasis. No thyroid tissue or pathological lymph node was detected after post-operative third-month thyroid and neck ultrasound.

Discussion

Primary thyroid lymphoma mostly originates from B-cell lineage. Of thyroid lymphomas, 60-80% are Diffuse Large B-Cell Lymphoma (DLBCL) followed by MALT lymphoma which represents nearly 10% to 23% of cases (4). MALT lymphoma is the third most common form of Non-Hodgkin Lymphoma (NHL) and accounts for 5-8% cases after DLBCL and follicular lymphomas (FL) (5). The incidence of the lymphoma is found almost equal in men and women and the average age recorded at the time of diagnosis is generally 60 years. Usually, two-third of the pa-

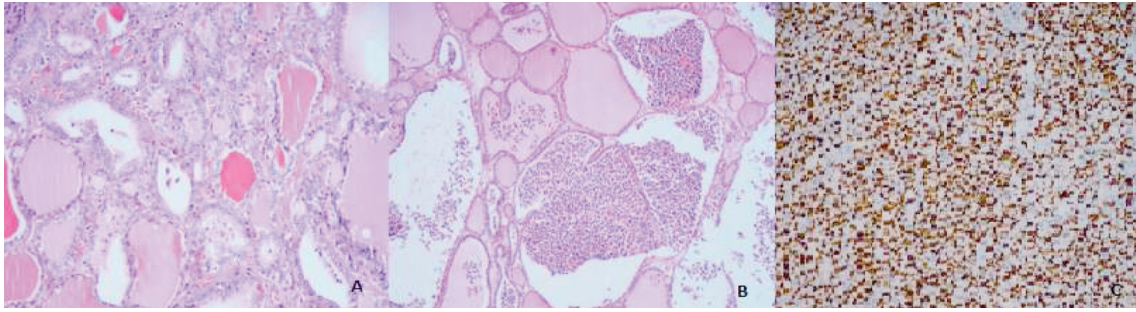


Figure 1: (A) Hematoxylin-eosin staining showing follicular variant papillary microcarcinoma (200x magnification) (B) lymphoid infiltrate filling the follicle lumen (100x magnification) and (C) Ki-67 proliferation index of the tumor was 90% (200x magnification).

tients are diagnosed with stage I-II disease, while only a few have more advanced disease. B symptoms are generally absent and involvement of bone marrow is rare.

MALT lymphomas rarely transform into a more aggressive lymphoma and usually turn out to form DLBCL (6). The lack of reliable biomarkers makes it difficult to diagnose histological transformation of the tissue. Transformed lymphomas are more difficult to manage than *de novo* aggressive lymphomas (7). Extranodal marginal zone lymphoma is commonly found in the gastrointestinal tract but may arise in tissues such as lung, thyroid, ocular adnexa, and breast. In most cases, the disease is localized to a primary site and regional lymph nodes (8).

MALT lymphoma is frequently coupled with autoimmune conditions (e.g., Sjögren syndrome, Hashimoto thyroiditis) or infections (*Helicobacter pylori* associated gastritis or hepatitis C). The presence of accompanying autoimmune disease causes lymphocytes to infiltrate the thyroid tissue (9,10).

A study published by Ling Chen *et al.* stated that Hashimoto's thyroiditis was present in 81.25% of patients, which included all patients with mucosa-associated lymphoid tissue (MALT) lymphoma. The study also stated that the incidence of Hashimoto's thyroiditis differed significantly among the four lymphoma groups: MALT, DLBL, MALT + DLBL, and small lymphocytic lymphoma ($P=0.014$) (11).

Although most cases have Hashimoto's thyroiditis in the background, it has been reported that MALT lymphoma can also develop as *de novo* without the presence of the former (12).

The first and important step in the diagnosis of thyroid lymphoma depends on the experience of the clinician and his ability to suspect the disease. Most patients with thyroid lymphoma exhibit symptoms such as goiter due to rapid growth of the thyroid gland and causes hoarseness due to compression. However, extranodal marginal zone lymphoma of MALT takes an indolent course. The diagnosis of extranodal marginal zone lymphoma may be delayed due to poor systemic symptoms. The occurrence of B symptoms and cytopenia is very rare in this disease (11,12).

Hematological tests along with few additional tests are required for patients with MALT lymphoma that are standard for patients with NHL required at the time of diagnosis. HCV and HIV testing are recommended for the patients, considering its association with MALT lymphoma. Other recommended tests include assessment of β_2 -microglobulin, serum protein electrophoresis, immunofixation, and serum-free light chain assay. For detection and staging of the disease, neck, thorax, abdomen, and pelvic CT scans and bone marrow biopsy should be taken into consideration. Since gastric involvement may be present in non-gastric MALT lymphomas, it is recommended to evaluate this aspect as well (13).

Herein, we presented a case with concomitance of thyroid papillary microcarcinoma and MALT in a background of Hashimoto's thyroiditis. In contrast to published reports, despite transformation to DLBCL, the patient in the present study was asymptomatic and further evaluated only for the presence of a considerable number of thyroid nodules.

After staging workup, bone marrow involvement with marginal zone lymphoma (not DLBCL) was revealed.

The prognosis of the extranodal marginal zone lymphoma of MALT localized to the thyroid is excellent and the 5-year disease-specific survival rates for it are more than 95%; however, it is known that patients with extrathyroidal invasion or transformation to high-grade lymphoma have a poor prognosis. In addition, current guidelines do not have the optimal treatment and standardized follow-up protocol (12). As a result, extranodal marginal zone lymphoma of the thyroid gland is rare and its pathogenesis is not fully understood. Despite the rarity of PTL, it can simultaneously exist with PTC, especially in patients with Hashimoto thyroiditis. The treatment for such cases has to be standardized and priority should be given to the stage and condition of the tumor.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Hakan Düğer, Murat Çalapkulu; Design: Hakan Düğer; Control/Supervision: Erman Çakal; Data Collection and/or Processing: Erman Çakal, Mustafa Özbek, Demet Yılmaz, Kutsal Doğan, Murat Çalapkulu, Bekir Uçan; Analysis and/or Interpretation: Hakan Düğer, Murat Çalapkulu, Muhammed Erkam Sencar; Literature Review: Hakan Düğer; Writing the Article: Hakan Düğer; Critical Review: Hakan Düğer,

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