

Original Article

Concomitant papillary thyroid carcinoma and mucosa-associated lymphoid tissue thyroid lymphoma in the setting of Hashimoto thyroiditis

Xia-Bin Lan^{1*}, Jun Cao^{1*}, Xu-Hang Zhu^{1*}, Zhe Han², Yu-Qing Huang^{1,4}, Ming-Hua Ge¹, Hai-Yan Yang³

Departments of ¹Head and Neck Surgery, ²Medical Imaging, ³Lymphoma, Zhejiang Cancer Hospital, Gongshu District, Hangzhou 310022, China; ⁴Zhejiang Chinese Medical University, Hangzhou, China. *Equal contributors.

Received March 7, 2018; Accepted April 13, 2018; Epub June 1, 2018; Published June 15, 2018

Abstract: The simultaneous occurrence of papillary thyroid carcinoma (PTC) and mucosa-associated lymphoid tissue (MALT) lymphoma of the thyroid gland is extremely rare, and many questions about their diagnosis and treatment remain unsolved. We report three cases of patients with both PTC and MALT thyroid lymphoma in the setting of Hashimoto thyroiditis (HT). Patient characteristics, pre-operative examination, histological findings, treatments, and follow-up were reviewed. In addition, we searched PubMed, Embase, and ISI Web of Science databases for articles published in the English language using the key words “lymphoma” and “thyroid”, and we reviewed almost all the reports about simultaneous occurrence of PTC and MALT thyroid lymphoma. In conclusion, PTC and MALT thyroid lymphoma can exist concomitantly, especially in patients with longstanding HT. These rare cases highlight the importance of close communication between clinicians, histopathologists, and radiologists to ensure that such rare cases are not missed; a multidisciplinary approach and careful surveillance are also needed.

Keywords: Papillary thyroid carcinoma, lymphoma, hashimoto thyroiditis, treatment

Introduction

Papillary thyroid carcinoma (PTC) is the most prevalent type of thyroid cancer, accounting for approximately 80%-90% of cases, whereas primary thyroid lymphoma (PTL) is very rare, accounting for only 0.6% to 5% of all thyroid cancers; and mucosa-associated lymphoid tissue (MALT) lymphoma is one of the most common subtypes [1]. PTC usually has an indolent biological behavior and a very favorable prognosis (20-year survival rate, >90%). MALT thyroid lymphoma also carries a good prognosis with a 5-year disease-specific survival rate >90% [2]. PTC has been described with Hashimoto's thyroiditis (HT), but it remains controversial [3] whereas MALT usually arises in a background of HT [1]; however, the simultaneous occurrence of both malignancies in the same patient is extremely rare. We describe three patients with HT and synchronous occurrence of PTC and MALT thyroid lymphoma. To our knowledge, this is one of the largest case series. As only eight such occurrences

have been reported in the literature [4-9], diagnosis and treatment of patients with PTC and MALT thyroid lymphoma is unclear. The aim of this study was to analyze the patients' clinicopathologic characteristics, treatments, and prognosis.

Clinical history

Patient 1

A 57-year-old man was referred to us for enlargement of his thyroid, revealed by neck ultrasonography (US) in November 2012. His medical history was unremarkable. On clinical examination, he had a palpable 4.0 cm nodule in the left lobe and 2.0 cm nodule in the right lobe. No other abnormal findings were detected. Routine laboratory tests were normal, and hormone evaluation showed euthyroidism but antithyroid antibodies were positive (anti-TPO, 54.9 IU/mL [normal range, 0 to 34 IU/mL]; anti-Tg, 1504.0 IU/mL [normal range, 0 to 115 IU/mL]). Thyroid US confirmed the presence of a

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multinodular goiter; the larger nodule was 4.0 cm in diameter, hypoechoic, and in the left lobe. Also, computed tomography (CT) scan detected multiple nodules.

In January 2013, the patient underwent left thyroidectomy and regional lymph node dissection, and right partial thyroidectomy. Histopathologic examination showed: a 0.8 cm papillary carcinoma in the left lobe with regional lymph node metastasis, and margin zone lymphoma of mucosa-associated lymphoid tissue (MALT) in the left and right lobe, and extensive lymphocytic infiltration of the thyroid parenchyma diagnostic of HT. Immunohistochemistry showed CK (+), CD20 (+), CD79a (+), CD10 (-), bcl-2 (+), bcl-6 (low +), Ki-67 (10% +), CD21 (+), CD3 (+), CD5 (+), CyclinD1 (-), CD43 (+), CD23 (+), Kappa/κ (+), Lambda/λ (+), which supports the diagnosis of MALT lymphoma. Postoperatively, thyroxine treatment was initiated and a staging procedure followed, including CT of head, chest, abdomen, and pelvis; serum protein electrophoresis; serum lactate dehydrogenase and β₂-microglobulin levels; and bone marrow biopsy, which was negative. Thus a stage of IE was confirmed based on the Ann Arbor staging. In May 2013, he accepted radiotherapy of 30Gy/15F in order to exterminate the residual lymphoma tissue. He was then treated with a thyroid-stimulating hormone (TSH)-suppressive dose of thyroxine. Follow-up evaluation for PTL and PTC was negative, and he remains asymptomatic now.

Patient 2

A 43-year-old woman was admitted to our hospital for thyroid cancer surgery in July 2013. She had no special medical history except hypothyroidism 2 year ago and accepted thyroxine replacement therapy. In May 2013, she went to another hospital for US examination which revealed a small calcific nodule in the isthmus of the thyroid gland. She underwent ultrasound-guided fine-needle aspiration (FNA) biopsy of this nodule and was diagnosed with PTC. Then she was referred to our hospital for thyroid operation. Routine laboratory tests were normal, and hormone evaluation showed euthyroidism but antithyroid antibodies were positive (anti-TPO, >600.0 IU/mL [normal range, 0 to 34 IU/mL]; anti-Tg, 149.3 IU/mL [normal range, 0 to 115 IU/mL]). Review of US revealed a palpable 1.4 cm calcific nodule in

the isthmus of the thyroid gland and showed extensive thyromegaly on both sides.

In July 2013, she underwent total thyroidectomy and bilateral regional lymph node dissection. Histopathologic examination showed: a 0.8 cm papillary carcinoma in the isthmus of the thyroid gland, and lymphoid tissue diffuse hyperplasia in the peripheral thyroid. Immunohistochemistry showed CK (+), EMA (+), CK19 (+), HBME1 (partial +), Gly-3/Glypican3 (-), CD20 (+), CD79a (+), CD3 (partial +), CD43 (partial +), CD5 (partial +), CD21 (+), CD23 (+), CD10 (-), bcl-6 (+), bcl-2 (-), Ki-67 (+, <10%), which supports the diagnosis of MALT lymphoma. CT scan of head, chest, abdomen, pelvis and bone marrow aspiration showed no evidence of lymphoma. Because PTL was confined to the thyroid (stage IE), and she had already undergone total thyroidectomy, no other treatment was recommended. The patient was then treated with post-operative thyroid hormone suppressive therapy. She is asymptomatic now.

Patient 3

A 61-year-old woman with thyroid enlargement of two years of duration was seen in our hospital for progressive enlargement of the thyroid gland without any discomfort. She had a history of cervical carcinoma and underwent radiation and chemotherapy with no relapse. Routine laboratory tests were normal and hormonal examination was normal too. However, antithyroid antibodies were positive (anti-TPO, 265.7 IU/mL [normal range, 0 to 34 IU/mL]; anti-Tg, 1000.0 IU/mL [normal range, 0 to 115 IU/mL]). Thyroid ultrasonography revealed a hypoechoic mass in the right thyroid lobe with diameter of 3.0 cm (TI-RADS 4b) and a small nodule in the left thyroid lobe (TI-RADS 2).

In December 2013, she underwent right thyroidectomy. Histopathologic examination showed two neoplastic lesions: a 0.15 cm papillary carcinoma, and lymphoid tissue diffuse hyperplasia in the rest of the right thyroid lobe. Immunohistochemical staining was performed: CD20 (+), CK (lymphoid epithelial lesions +), CD79a (+), CD3 (separately +), CD5 (separately +), CD21 (+), CD23 (+), CD43 (separately +), CD10 (-), bcl-6 (partly low +), bcl-2 (partly +), Ki-67 (20%-30% +), CyclinD1 (-), Kappa/κ (+), Lambda/λ (+), which supports the diagnosis of MALT lymphoma. Positron emission computed

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Table 1. Summary of prior reported cases of coexisting PTC and MALT thyroid lymphoma

Series (references)	Age (years)/sex	Clinical presentation	HT	Discovery method	Stage of MALT thyroid lymphoma	Treatment	Prognosis
Derringer et al. [4]	3 patients	NA	NA	NA	NA	NA	NA
De Melo et al. [5]	61/Male	Fast thyroid enlargement	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery and radioactive iodine	No recurrence in 2.0 years
Vassilatou et al. [6]	51/Female	A palpable 2.0-cm nodule in the right lobe	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery and radioactive iodine	No recurrence in 14 months
Cheng et al. [7]	59/Male	Multiple thyroid nodules	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery and radioactive iodine	No recurrence in 7.0 years
Nam et al. [8]	81/Female	Thyroid nodule and hoarseness	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery	No recurrence in 1.0 year
Shen et al. [9]	25/Female	A palpable 1.2-cm nodule in the right lobe	Yes	Postoperative pathological examination	Stage IE	Surgery, radioactive iodine and chemotherapy	No recurrence in 2.0 years
Cao et al. (our study)	57/Male	A palpable 4.0-cm nodule in the left lobe and 2.0 cm nodule in the right lobe.	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery and radiotherapy	No recurrence in 4.5 years
	43/Female	Nothing unusual	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery	No recurrence in 4.0 years
	61/Female	A palpable 3.0-cm nodule in the right lobe	Yes	Postoperative pathological examination and IHC	Stage IE	Surgery and radiotherapy	No recurrence in 3.5 years

(NA) not available, (PTC) papillary thyroid carcinoma, (MALT) mucosa-associated lymphoid tissue, HT (hashimoto's Thyroiditis), IHC (immunohistochemical).

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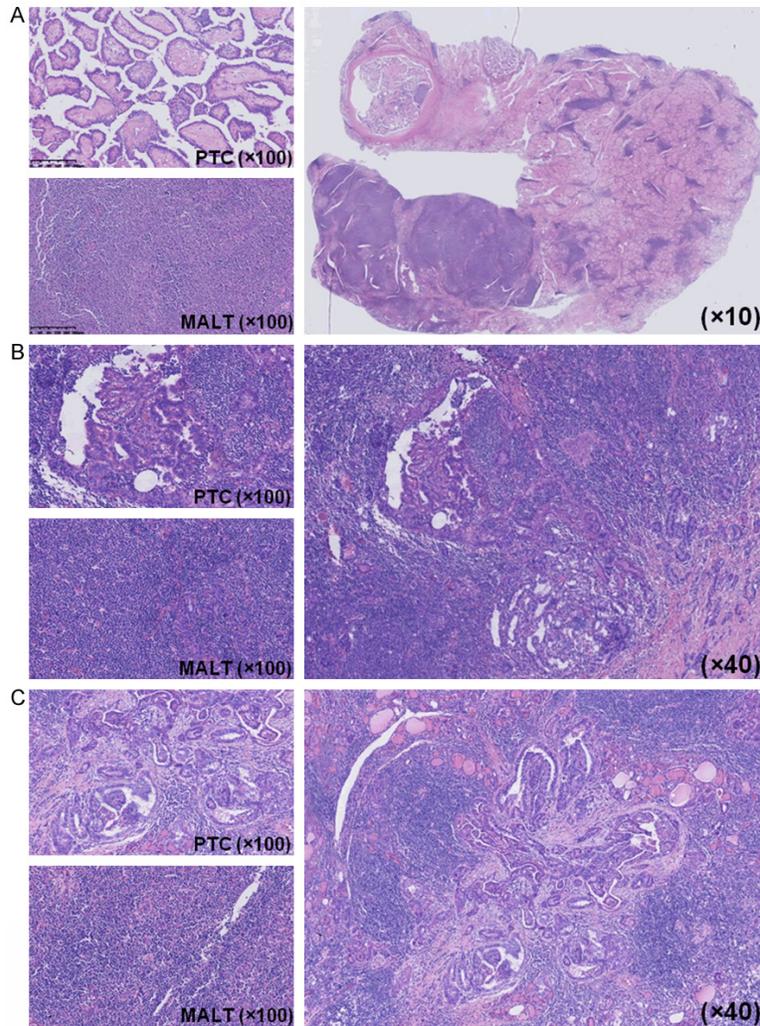


Figure 1. Hematoxylin and eosin (HE) staining of patients with concomitant papillary thyroid carcinoma (PTC) and mucosa-associated lymphoid tissue (MALT) thyroid lymphoma. A. Patient 1; B. Patient 2; C. Patient 3.

tomography (PET-CT) showed metabolism was slightly higher in the left thyroid tissue and the right residual thyroid tissue. Followed CT scan of head, chest, abdomen, pelvis, and bone marrow aspiration were negative. Thus, a stage of IE was established. In January 2014, she accepted radiotherapy of 30Gy/10F in order to extinguish the residual lymphoma. Follow-up evaluation for PTL and PTC was negative, and the patient remains asymptomatic until now.

Materials and methods

The prospectively maintained institutional database at Zhejiang Cancer Hospital was retrospectively searched for patients with simultaneous occurrence of PTC and PTL in the period of 1996-2015. The demographic data, present-

ing symptoms, pathology findings, and types of treatment, and clinical outcome were documented (**Table 1**). Three patients with simultaneous occurrence of PTC and MALT thyroid lymphoma were identified. All pathologic specimens were reviewed by a single experienced pathologist, and all diagnoses were rendered based on morphologic features, and further confirmed by immunohistochemistry (IHC). The specimens were fixed in 10% formalin and embedded in paraffin, and 4- μ m-thick slices were prepared for hematoxylin and eosin staining and IHC. The IHC stains were performed on an automated immunostainer (Leica, Bondmax, Germany). Follow-up occurred until June 2017. In addition, we searched PubMed, Embase, and ISI Web of Science databases for articles published in the English language using the key words "lymphoma", and "thyroid", and we reviewed almost all the reports about simultaneous occurrence of PTC and MALT thyroid lymphoma. All the patients signed informed consent, and this study was performed with the

approval of the Ethics Committee of Zhejiang Cancer Hospital.

Results

We report three patients with simultaneous occurrence of PTC and MALT thyroid lymphoma. They include one man and two women between 43 to 61 years old at the time of diagnosis. The clinical data of the patients are summarized in **Table 1**. Patients presented with nonspecific symptoms such as fever, nocturnal sweating and weight loss more than 10%, except one patient presented with hypothyroidism 2 year ago. Preoperative imaging such as neck ultrasound, CT and even PET-CT cannot exclude a compressive goiter. Only one patient underwent preoperative FNA, but diagnosis of MALT lymphoma

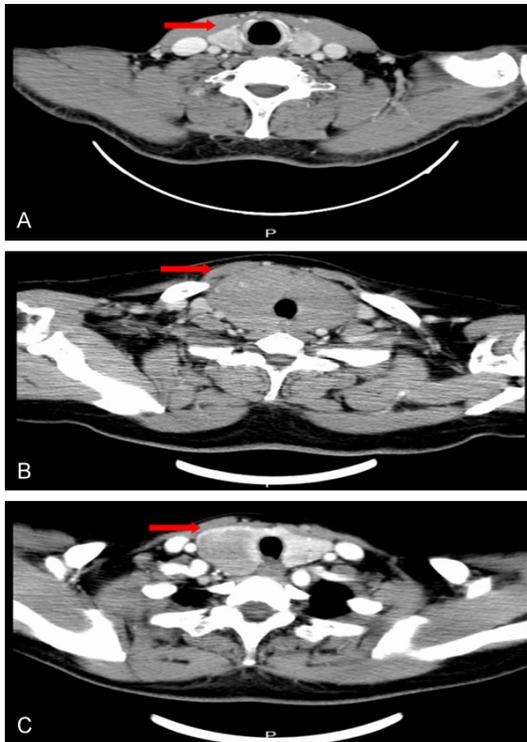


Figure 2. Contrast-enhanced computed tomography (CT) scans of patients concomitant PTC and MALT thyroid lymphoma. A. Patient 1: Mildly enhanced nodular foci in the bilateral thyroid gland lobes, and no enlarged lymph nodes were seen around (arrow); B. Patient 2: A large, inhomogeneous enhancement of the whole thyroid gland, and the trachea was slightly compressed, and no enlarged lymph nodes were seen around (arrow); C. Patient 3: A large, inhomogeneous enhancement of the right thyroid gland, with clear border, and no enlarged lymph nodes were seen around (arrow).

phoma was not made. MALT thyroid lymphomas were all discovered after surgery. The whole surgical specimen was submitted to routine histopathologic evaluation, cytology and immunohistochemistry, and the pathologic types of TC and PTL were defined based on the current WHO criteria. MALT thyroid lymphoma showed reactive germinal centers, lymphoepithelial lesions, and frequent plasmacytic differentiation (**Figure 1**). PTC showed papillary architecture, sheets, and microfollicles with characteristic nuclear features such as pale powdery chromatin, grooves, nuclear enlargement, small but distinct nucleoli, and intranuclear cytoplasmic inclusions (**Figure 1**). MALT thyroid lymphomas were all confined to the thyroid gland, and were all staged as IE (localized disease). One patient was treated by surgical resection alone (patient 2), and two patients were treated by surgical resection and radio-

therapy (patient 1 and 3), and all the patients were treated with post-operative thyroid hormone suppressive therapy. Follow-up evaluation for them was negative, and the patients remain asymptomatic now.

Discussion

PTL is a lymphoma originating from the thyroid, not including lymphoma metastases to the thyroid and a direct violation of cervical lymph node disease. PTL is very rare, accounting for 0.6% to 5% of all thyroid cancers, and 2% of extranodal lymphomas [10]. Almost all cases are of B-cell origin, and MALT lymphoma is one of the most common subtypes [1]. MALT thyroid lymphoma occurs more frequently in the middle-aged to older individuals, predominantly female. It tends to have an indolent course and carries a good prognosis with a 5-year disease-specific survival rate >90% [2]. PTC, which is the most common variant of thyroid cancer, also has an excellent prognosis (20-year survival rate, >90%), and its co-occurrence with MALT lymphoma is very rare, with only a few case reports found in literature (**Table 1**).

Synchronous appearance of two primary tumors of different histology in the same organ has been rarely described. PTC has been reported as being associated with HT in 10%-58% of cases [11, 12], however, an association between HT and PTC is still debated [3]. Some molecular studies have suggested that various alterations of oncogenes like RET/PTC gene rearrangement may regulate the early stages of tumor development and inflammation of the thyroid [12, 13]; however, many additional, still unknown steps are probably required for oncogenic transformation [14]. A vast majority of cases of MALT thyroid lymphoma arise in the setting of HT [1], as in our patients. The relative risk of developing a thyroid lymphoma has been estimated as being 67-80 times higher in patients with HT compared with the general population [4], even though MALT lymphoma occurs in 0.5% of the cases [15]. The malignant evolution process is difficult to characterize, attributable to indolent growth and long period duration for examining clinical and morphologic findings. Some indirect molecular findings suggest that prolonged antigenic stimulation in the setting of autoimmune thyroiditis could lead to lymphomatous transformation, similar to the pathogenesis of primary extranodal non-Hodgkin's lymphoma of the salivary glands and

stomach [16]. Moreover, aberrant somatic hypermutation process, which is considered a mechanism of lymphomagenesis, has been shown in non-neoplastic B-cells from chronic lymphocytic thyroiditis and in PTL. These findings suggested that malfunction of the somatic hypermutation process represents an early event in the process of B-cell clonal transformation [16, 17]. There are no data linking PTC and MALT thyroid lymphoma. However, because HT is the only known risk factor for development of MALT thyroid lymphoma and may favor development of PTC in certain individuals, a simultaneous occurrence in this context could be a possible, albeit rare, event. Furthermore, all of our patients suffer from HT. Thus, these cases can be considered special examples of the implication of HT in thyroid tumorigenesis.

The clinical diagnosis of primary MALT thyroid lymphoma is relatively difficult. Differential diagnosis between primary MALT thyroid lymphoma and generalized lymphoma with thyroid involvement must be made. Clinical examination usually reveals rapid growth of a hard, fixed, and frequently unilateral thyroid nodule, sometimes with compressive symptoms [18]. B symptoms like fever, nocturnal sweating, and weight loss more than 10% suggests typical disseminated lymphoma, either primary in the thyroid gland or at other sites. Preoperative exams such as neck ultrasound, CT and even PET-CT can be indistinguishable from compressive goiter (**Figure 2**). While diagnosis of diffuse large B-cell lymphoma by FNA is often straightforward, the diagnosis of MALT thyroid lymphoma is difficult, especially in the setting of HT, as both diseases have similar histologic characteristics, including plasma cell differentiation, infiltration by B-cells, and lymphoepithelial lesions [19]. In our study, only one patient underwent preoperative FNA, but it failed to make a diagnosis of MALT lymphoma. MALT thyroid lymphoma may be an incidental finding on histology, as all cases in our patients were discovered after surgery. Thus, an adequate specimen is essential for a correct diagnosis, although nowadays FNA with flow cytometry has been proved useful in some cases [18]. The whole surgical specimen was submitted to routine histopathologic evaluation, cytology, and immunophenotyping by flow cytometry and immunohistochemistry. Diagnostic features of MALT lymphoma include reactivation germinal centers, lymphoepithelial lesions, and frequent plasmacytic differentiation [1]. On the contrary,

the diagnosis of PTC is relatively easy. Some typical findings include microcalcifications, poorly defined borders, irregular shape, and intranodal vascularity on doppler ultrasonography increase the suspicion of PTC [20]. In addition, PTC has distinct cytologic features of papillary architecture, sheets, and microfollicles with characteristic nuclear features such as pale powdery chromatin, grooves, nuclear enlargement, small but distinct nucleoli, and intranuclear cytoplasmic inclusions [21].

Patients with concomitant MALT thyroid lymphoma and PTC, very rare in the literature, make it a challenge in management and follow-up. Treatment must be tailored individually, needing a comprehensive knowledge of both diseases to guide optimal management. Treatment options of patients with MALT thyroid lymphoma remain controversial and a correct stage must be determined with complete physical exam, laboratory examination, chest, neck, abdomen CT, bone marrow biopsy to ensure optimal treatment. In addition, PET-CT has been considered as an elective exam in the setting of the lymphoma stage, and evaluation of clinical response for specific treatment [22]. The Ann Arbor classification for primary thyroid lymphoma was modified by Mussoff [23]: stage IE of lymphoma is usually localized to the thyroid gland; stage IIE of lymphoma is localized to the thyroid and the regional lymph nodes on the same side of the diaphragm; stage IIIE of lymphoma is localized to the thyroid gland and lymph nodes on both sides of the diaphragm and/or spleen; and stage IV refers to disease in nodal and/or additional extranodal involvement. Stage IE and IIE disease were regarded as localized disease, and stage IIIE and IV disease were regarded as disseminated disease. The treatment of MALT thyroid lymphoma may comprise different modalities (eg, surgery, radiotherapy, chemotherapy) [1, 15]. Currently, surgical resection is recommended only for patients with lymphoma limited to the thyroid gland and is often curative [24]. When there is spread outside of the thyroid, surgical resection is performed only for biopsy [24, 25]. If the disease is a localized disease, disease-free and overall survival estimates after total thyroidectomy for MALT thyroid lymphoma are 100% at 5 years [4, 15]. However, for patients with lymphoma confined to the thyroid gland, the primary treatment option is radiotherapy. Tsang et al. reviewed 13 cases of localized (stage IE or IIE) extranodal MALT thyroid lymphoma.

phoma. They were treated with radiation therapy alone, and had a 100% disease control rate [26]. Furthermore, another two studies report very high disease-free survival rate and cure rate in patients with lymphoma confined to the thyroid gland and treated with thyroidectomy and subsequent radiotherapy [27, 28]. In addition, multimodality therapy (surgery plus radio- or chemotherapy) is recommended in some institutions with curative intent [29, 30], and chemotherapy is classically indicated for advanced disease, such as locally aggressive or disseminated lymphoma. But its role in localized disease is not clear [30]. In our patients, MALT thyroid lymphomas were all confined to the thyroid gland, and were all staged as IE (localized disease), so surgical resection alone seemed adequate (patient 2). However, in patient 1 and 3, they did not undergo total thyroidectomy, so radiotherapy was critical to extinguish the residual invisible lymphoma. Because some retrospective reports in patients with other extranodal MALT lymphomas have documented the dissemination of disease in about one-third of cases at the time of diagnosis [15]. No chemotherapy was needed in the postoperative period because there was no lymph-node retention and no systemic spread. Furthermore, surgery is the mainstay of treatment and is often curative for papillary thyroid microcarcinoma. In the event that MALT thyroid lymphoma and PTC do coexist, treatment strategies should be individualized, and the management has to prioritize the tumor which presents a worse prognosis at moment, but ideal therapy entails optimal treatment of both diseases. In addition, the prognosis is probably affected by the one having a worse stage. MALT thyroid lymphoma tends to have an indolent course and carries a good prognosis with a 5-year disease-specific survival rate >90%, but about 40% of diffuse B-cell lymphoma appears to evolve from MALT lymphoma [2], and the overall 5-year survival of diffuse B-cell lymphoma is <50%. Thus, close follow-up is very important.

Conclusions

Patients with concomitant MALT thyroid lymphoma and PTC are very rare. Preoperative exams such as neck ultrasound, CT and even PET-CT can be indistinguishable for MALT thyroid lymphoma, and the cytological diagnosis of MALT thyroid lymphoma may be difficult. Thus,

MALT thyroid lymphoma may be an incidental finding on histology after surgery. However, despite the rarity of MALT thyroid lymphoma, it has to be taken into consideration with masses growing rapidly and who have a history of HT. A patient presenting with concomitant MALT thyroid lymphoma and PTC must be judiciously evaluated, since the management must prioritize the tumor that presents a worse prognosis. Herein, we report three cases of MALT thyroid lymphoma and PTC coexisted in the setting of HT. These case reports have the aim to add to the experience of this rare disease.

Acknowledgements

This study was funded by the National Natural Science Foundation of China (Grant Number: 81702653 and 81672642).

Disclosure of conflict of interest

None.

Address correspondence to: Hai-Yan Yang, Department of Lymphoma, Zhejiang Cancer Hospital, 1 Banshan East Road, Gongshu District, Hangzhou 310022, China. E-mail: yanghaiyan@zjcc.org.cn; Ming-Hua Ge, Department of Head and Neck Surgery, Zhejiang Cancer Hospital, 1 Banshan East Road, Gongshu District, Hangzhou 310022, China. E-mail: gemh@zjcc.org.cn

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