Mucosa-Associated Lymphoid Tissue Lymphoma of the Thyroid Gland: A Systematic Review of the Literature

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Keywords

Mucosa-associated lymphoid tissue · Thyroid · Marginal zone B-cell lymphoma · Lymphoma · Hashimoto thyroiditis

Abstract

Objective: Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type of the thyroid gland is a rare indolent malignant disease encountered in approximately 0.5% of patients with Hashimoto thyroiditis (HT). The purpose of the present systematic review was to accumulate the current evidence in the field. **Study Design:** We searched the Medline, Scopus, EMBASE, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials CENTRAL databases from inception to May 2018. Statistical analysis was performed with SPSS version 22.0. **Results:** Fourteen case series and 20 case reports were finally included in the present systematic review. Analysis of the patient data included in the published case reports suggested that the age at diagnosis of MALT lymphoma does not differ among males and females (64 [52.5–73] vs. 67 [60.5–72] years, $p = 0.442$). HT was detected in 60% of patients, whereas coexisting carcinoma was evident in 17% of cases. The incidence of HT and thyroid cancer was comparable among

males and females ($p = 0.474$ and $p > 0.999$, respectively). Among all patients included in the present systematic review there were two disease relapses and two deaths attributed to the disease. **Conclusion:** MALT lymphoma of the thyroid gland is a rare malignancy with an indolent course. The scarce data available in the literature preclude safe conclusions concerning the mode of treatment and follow-up of these patients. However, the combination of minimally invasive surgery and adjuvant therapy seems feasible. Moreover, an extended follow-up period is recommended.

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Introduction

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type is a rare disease characterized by morphologically heterogeneous B-cells. The majority of cases refer to lymphomas of the gastrointestinal tract; however, other organs may also be affected. A prerequisite for the occurrence of MALT lymphoma is abundance of lymphoid tissue in the affected organ; therefore, it is usually seen in the salivary gland, the thyroid, the eye, the skin, and the thymus gland.

Fig. 1. Search plot diagram.

MALT lymphoma of the thyroid gland is rarely reported in the literature as its incidence is significantly lower than that of other organs [1, 2]. Compared to diffuse large B-cell lymphoma (DLBCL), MALT lymphoma is less common. Specifically, previous studies suggest that DLBCL accounts for >50% of thyroid lymphomas, whereas the incidence of MALT is believed to range between 10 and 23% [3, 4]. Given its rarity, there is still no firm consensus on the diagnostic and therapeutic approach to affected patients.

The purpose of the present systematic review was to accumulate current evidence in the field related to the diagnosis, management, and follow-up of patients with thyroid MALT lymphoma.

Methods

Study Design

The present meta-analysis was designed according to the PRISMA guidelines [5]. Eligibility criteria were predetermined by the authors. Date restrictions were applied during the literature search. We also sought to avoid language restrictions; however, studies in languages that are based on ideograms (Chinese, Arabic, etc.) were excluded when Google translate could not be used safely to extract data. All types of observational studies (prospective and retrospective) that included information related to thyroid MALT lymphoma were held eligible for inclusion. Case series and case reports were also included, while controlled

studies (randomized or nonrandomized) are missing due to the rarity of the disease. The studies were selected in three consecutive stages. Two authors (I.K., A.A.) screened the titles and/or abstracts of all electronic articles to assess their eligibility. All the articles that met or that were presumed to meet the criteria were retrieved in full text. In the final stage, after carefully reading the full-text articles, the authors selected all relevant clinical observational studies (both prospective and retrospective) for tabulation. Review articles were excluded from tabulation and analysis of results. Both researchers tabulated the selected indices in structured forms. Any discrepancies in the methodology, retrieval of articles, and statistical analysis were resolved by consensus of all authors.

Literature Search and Data Collection

We used the Medline (1966–2019), Scopus (2004–2019), EMBASE, ClinicalTrials.gov (2008–2019), and Cochrane Central Register of Controlled Trials CENTRAL (1999–2019) databases in our primary search, along with the reference lists of electronically retrieved full-text papers. The date of last search was February 28, 2019. Our search was restricted to a minimum number of keywords in order to assess an eligible number that could be hand searched, minimizing potential loss of articles. All the articles that met or were presumed to meet the inclusion criteria were retrieved in full text. Our search strategy included the words “MALT,” “MZBL,” “lymphoma,” and “thyroid” and is presented schematically in Figure 1.

Quality Assessment

We evaluated the methodological quality of included case series and case reports based on the tool proposed by Murad et al. [6]. The tool briefly assesses the selection of patients, the ascertain-

Table 1. Assessment of the methodological quality of the case reports

Reference (first author)	Selection	Ascertainment		Causality	Reporting	Overall
		exposure	outcome	follow-up		
Shrestha, 2018 [27]	–	★	–	–	★	2
Mizokami, 2016 [28]	★	★	★	– ^a	★	4
Jeon, 2016 [29]	★	★	–	–	–	2
Diaconescu, 2016 [30]	–	★	★	–	★	3
Shen, 2015 [31]	–	★	★	–	★	3
Yang, 2015 [32]	★	★	★	★	★	5
Hengjeerajarus, 2015 [33]	–	★	–	–	★	2
Tarui, 2014 [34]	–	★	★	–	★	3
Nam, 2013 [35]	–	★	★	–	★	3
Binesh, 2011 [36]	–	★	★	–	★	3
Melo, 2010 [37]	–	★	★	–	★	3
Kojima, 2009 [38]	–	★	★	–	★	3
Kojima, 2009 [39]	–	★	★	– ^a	★	4
Licci, 2008 [40]	–	★	★	–	–	2
Colović, 2007 [41]	★	★	★	– ^a	★	5
Castronovo, 2005 [42]	–	★	★	–	–	2
Shah, 2004 [43]	–	★	★	–	–	2
Trouette, 2002 [44]	–	★	★	–	★	3
Gogas, 2002 [45]	–	★	–	–	★	2
Ghazanfar, 2002 [46]	–	★	–	–	★	2

^a The adequacy of the follow-up period was documented, but not in all cases.

ment of exposure, the causality (which was translated in our study as the efficacy of the follow-up period that was used in determining the 5-year survival rates), and reporting measures (extent of reporting and detailed information that allow replication of the data in future studies for reasons of validation).

Statistical Analysis

We performed quantitative analysis to determine the potential differences in terms of simultaneous presence of Hashimoto thyroiditis (HT), invasive thyroid cancer, and age among the two sexes. The Mann-Whitney U test was used to compare median values between groups due to their nonnormal distribution. Results of continuous variables are presented as median (interquartile range). For comparisons of proportions, we used the χ^2 and Fisher exact tests. All reported analyses were designed as two-tailed. Statistical significance was set at $p < 0.05$. The IBM SPSS Statistics for Windows, version 22.0 statistical package (released 2013; IBM Corp., Armonk, NY, USA) was used in this study.

Results

Excluded Studies

Overall, 9 studies were excluded from the present systematic review after reading their full text. Their majority either did not investigate outcomes related to thyroid

MALT lymphomas or did not report the outcomes of interest that were investigated in the present study (Tables 1, 2) [7–14]. One study was also excluded because it was written in Chinese and safe translation was not possible [15].

Included Studies

Fourteen case series [1–3, 16–26] and 20 case reports [27–46] were finally included. The quality assessment of these studies indicated that case reports were significantly inferior compared to case series in terms of patient selection ($p = 0.032$).

Outcomes from Case Reports

Table 3 summarizes the outcomes that were evaluated in the present systematic review. Tabulated data are based mostly on case reports, as the majority of data from case series were aggregated, hence precluding tabulation. Overall, 25 females and 9 males were reported in the case reports (Table 1). Data related to patients' sex included in the case series were scarce and not analyzed. The age at diagnosis of MALT lymphoma did not differ among males and females that were mentioned in the case reports (64 [52.5–73] vs. 67 [60.5–72] years, $p = 0.442$) (Table 3). HT

Table 2. Assessment of the methodological quality of the case series

Reference (first author)	Selection	Ascertainment		Causality	Reporting	Overall
		exposure	outcome	follow-up		
Watanabe, 2018 [16]	★	★	★	★	★	5
Teckie, 2017 [1]	★	★	★	★	★	5
Hirokawa, 2017 [17]	★	★	–	–	★	3
Bostanci, 2017 [18]	★	★	★	–	★	4
Chai, 2015 [19]	★	★	★	–	★	4
Cha, 2013 [20]	★	★	★	–	★	4
Oh, 2012 [21]	★	★	★	★ ^a	★	5
Lee, 2011 [22]	★	★	★	★ ^a	★	5
Munemasa, 2009 [23]	★	★	–	–	★	3
Suh, 2008 [2]	★	★	★	–	★	4
Kuper-Hommel, 2005 [3]	★	★	★	– ^b	★	4
Thieblemont, 2002 [24]	★	★	★	–	★	4
Tsang, 2001 [25]	★	★	★	– ^b	★	4
Derringer, 2000 [26]	★	★	★	– ^b	★	4

^a 5-year overall survival rates were partially reported in these studies. ^b 2-year overall survival rates were reported in this study.

was detected in 72% of patients, whereas coexisting carcinoma was evident in 7% of cases. The incidence of thyroid cancer was comparable among the two sexes ($p > 0.586$). HT was, however, more prevalent among women ($p = 0.004$). According to immunohistochemical analysis, 14 out of 25 tissues stained positively for CD20, while it was 5 for CD43 and 3 for CD21. The presence of goiter or an enlarging painless mass was the most frequent clinical finding, whereas hoarseness and shortness of breath were less frequent.

The majority of cases presented in stage IA according to the Ann Arbor classification for extranodal MALT lymphoma. The implemented modes of treatment varied significantly among the included studies. Only 5 patients underwent lymph node dissection (either satellite lymph node dissection or modified radical neck dissection) (Table 3). Hemithyroidectomy or lobectomy was reported in 17 cases and total thyroidectomy in 12 cases. One case was diagnosed with open biopsy and then treated with radiotherapy. The majority of the patients had favorable outcomes, as only 3 deaths were reported [32]. One of the patients died from pancreatic cancer rather than disease relapse [25]. A second patient died within 10 years from diagnosis, but at 5 years she was still alive with no evidence of relapse [32]. Specific patient characteristics that could potentially imply disease relapse were not identified.

Outcomes from Case Series

Various methods were used for histopathological diagnosis of MALT lymphoma in the included studies, ranging from fine needle aspiration to thyroidectomy (subtotal or total). They specifically mentioned that the specimen that is obtained by means of fine needle aspiration is too small to reach definitive conclusions, particularly when early lesions are present. The sensitivity and specificity of ultrasound was also extremely limited in the series, rendering the differential diagnosis of DLBCL from MALT lymphoma extremely inaccurate.

In 2000, Derringer et al. [26] reported the indolent course of MALT lymphoma of the thyroid. In their series none of the patients had evidence of disease relapse, whereas the outcomes were less favorable for patients with mixed DLBCL and MALT lymphoma and patients with DLBCL lymphoma. Moreover, they reported that none of the patients staged as IIIE and IVE had MALT lymphoma alone. Tsang et al. [25] followed the course of disease in patients with stage I and II MALT lymphoma at various sites and reported that those with gastric and MALT lymphomas had significantly better early outcomes compared to those with disease at other sites.

Of all case series included in the present systematic review, only Teckie et al. [1] reported the presence of two relapses (one in the larynx and the paratracheal lymph nodes and another one in the tongue). However, data concerning the survival of these patients were ab-

Table 3. Reported outcomes of the patients included in the case report studies

Reference (first author)	Age/sex	HT/TC	IHC+	Symptoms	Stage (therapy)	Surgery	TSH/TPO/Tg
Shrestha, 2018 [27]	60/m	+/-	CD20, CD79, CD43, CD45	routine	IAE (R ^a)	ST	10.14
Mizokami, 2016 [28]	70/f	+/-	NA	goiter	IE (R)	ST	0.02/+/+
	66/f	+/-	NA	none	IIE (R)	ST	0.24/+/-
	67/f	+/-	NA	none	IE (R)	biopsy	2.87/+/-
	67/f	+/-	NA	none	IE (R)	ST	1.09/+/+
	53/f	+/-	NA	none	IIE (R)	ST	3.60/+/-
	75/f	+/-	NA	none	IE (R)	ST	2.21/-/+
	73/f	+/-	NA	none	IE (R)	ST	1.77/+/+
	85/f	+/-	NA	none	IE	ST	5.40/+/+
	85/f	+/-	NA	none	IE	ST	2.93/-/+
Jeon, 2016 [29]	45/f	+/-	CD20, cytokeratin	goiter	IIIE (RCHOP)	TT MRND	7.89/-/-
Diaconescu, 2016 [30]	42/f	+/-	CD45	pain, hoarseness, shortness of breath	IAE (CHOP)	ST SLND	normal
Shen, 2015 [31]	25/f	+/-	NA	routine	IAE (CHOP)	TT	1.99/+/+
Yang, 2015 [32]	74/m	-/-	CD20, CD5, CD21, Bcl2	pain, hoarseness, shortness of breath	NA (CHOP+R)	NA	3.21/-/-
	73/f	+/-	CD20, CD5, CD21, Bcl2	hyperthyroidism, suffocation	NA (CHOP+R)	NA	3.04/+/+
	61/m	-/-	CD20, CD5, CD21, Bcl2	neck mass	NA (CHOP+R)	NA	37.83/-/-
Hengjeerajarus, 2015 [33]	70/m	+/-	CD20	goiter, shortness of breath	IIE (RCHOP)	no	85.12/+/-
Tarui, 2014 [34]	58/f	-/+	CD20	goiter	IE (-)	TT ND	NA
Nam, 2013 [35]	81/f	+/+	CD20	goiter, hoarseness	IE (-)	TT MRND	0.79/+/-
Binesh, 2011 [36]	69/m	+/-	CD20, CD138	goiter	IAE (R)	ST	NA
de Melo, 2010 [37]	61/m	+/+	CD20, CD79, CD43, E1/AE3	goiter	IAE	TT	NA
Kojima, 2009 [38]	82/m	+/-	NA	painless mass	IAE (-)	ST	73/NA/NA
	78/f	NA	NA	painless mass	IAE (-)	ST	NA
Kojima, 2009 [39]	50/f	NA	NA	goiter	NA (-)	TT	euthyroid/+
	46/f	NA	NA	goiter	NA (-)	ST	hypothyroid/+
	66/f	NA	NA	goiter	NA (-)	ST	euthyroid/+
Licci, 2008 [40]	55/f	+/-	CD20, CD43	goiter	NA (R)	TT	NA
Colović, 2007 [41]	62/f	-/-	CD43	painless mass	IE (-)	TT	NA
	62/f	-/-	CD43	painless mass	IE (CHOP)	TT MRND	NA
Castronovo, 2005 [42]	52/f	-/-	NA	painless mass	IE (R)	TT	NA
Shah, 2004 [43]	64/f	-/-	NA	painless mass	IE (-)	ST	NA
Trouette, 2002 [44]	67/m	-/-	CD79, CD20	goiter, hoarseness, pruritus	NA (-)	TT	normal/-/-
Gogas, 2002 [45]	56/m	+/-	CD20	goiter, dysphagia	NA	TT	normal/NA/NA
Ghazanfar, 2002 [46]	55/f	-/-	CD20	goiter, fever, fatigue	IE (NA)	ST	normal/-/-

-, negative; CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; HT, Hashimoto thyroiditis; IHC, immunohistochemistry; MRND, modified radical neck dissection; NA, data not available; ND, node dissection (extent not defined); R, radiotherapy; RCHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; SLND, satellite lymph node dissection; ST, subtotal thyroidectomy/hemithyroidectomy/lobectomy/partial lobectomy; TC, thyroid cancer; Tg, thyroglobulin; TPO, thyroperoxidase; TSH, thyroid-stimulating hormone; TT, total thyroidectomy. ^aThe patient deferred further therapy.

sent. Another study reported the death of a patient with MALT lymphoma, but the cause was unrelated to the disease [22].

Discussion

The findings of our study suggest that MALT lymphoma of the thyroid gland is characterized by an indolent course, as the vast majority of patients included among published case reports and case series were alive with no evidence of disease. Tsang et al. [25] already emphasized this in 2001 and reported that the follow-up of these patients should extend beyond 5 years. This finding is also supported by the single study that followed up all patients for at least 10 years and showed a case that relapsed beyond the expected 5 years [32].

The diagnosis of thyroid MALT lymphoma can be challenging. Kaba et al. [47] introduced specific cytological criteria in 2015. They specifically mentioned that a frequency of plasma cells <15% was associated with an 97% accuracy in distinguishing MALT from HT. Recently, however, Hirokawa et al. [17] suggested that fine needle aspiration is not sufficient to approach patients when MALT lymphoma is suspected, because it is accompanied by false-negative results that may reach 20%. Our review depicts the high prevalence of CD20 positivity in thyroid MALT lymphoma; however, to date it remains unknown whether this biomarker can be used to distinguish MALT from HT, as current evidence in this field remains limited [48].

Although the pathophysiology of MALT lymphoma of the thyroid gland has not been investigated thoroughly, Kuper-Hommel et al. [3] suggested that MALT lymphomas arise as a response to autoimmune processes, such as in patients with *Helicobacter pylori* infection and patients with HT. They specifically suggested that the prolonged autoimmune inflammation process in the thyroid may result in the growth of a pathological clone which could in turn lead to a progressive replacement of the normal lymphoid cell line, giving rise to MALT lymphoma. In 2009, Munemasa et al. [23] investigated the B-cell response to thyroglobulin; immunohistochemical analysis of MALT lesions indicated that thyroglobulin was present in the follicular dendritic cells of the germinal center of the thyroid MALT lymphoma. Since then, however, no further evidence concerning the pathophysiologic interaction of HT and MALT has been published. In our systematic review of case reports, we observed that the prevalence of HT was high, with no differences among the two

sexes. This evidence clearly depicts that the impact of HT is independent of sex, putting men and women who suffer from HT at the same risk of developing MALT lymphoma.

The various treatment modalities that were reported in the present systematic review were associated with an equally favorable outcome. Therefore, it would be prudent to suggest that radical surgery does not seem to benefit these patients and that once excisional biopsy has confirmed the presence of MALT lymphoma and ruled out the presence of DLBCL lymphoma or thyroid cancer, adjuvant therapy would suffice for these patients. However, given the scarce data in the literature, firm conclusions are precluded in this particular field as selection bias is an issue, particularly among published case reports (Table 1).

Conclusion

Despite the available clinical evidence, firm conclusions are precluded concerning the mode of treatment and follow-up of patients with MALT lymphoma of the thyroid gland. However, it seems that a combination of minimally invasive surgical techniques and adjuvant therapy would be prudent, at least for patients with stage IE and IIE disease, combined with an extended follow-up period. Given the low incidence of the disease, randomized trials are very hard to accomplish; however, the establishment of an international databank would be prudent to accumulate knowledge from various centers.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Disclosure Statement

The authors report that they have no conflicts of interest to disclose.

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