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Primary Thyroid Lymphoma: A Comprehensive Review of Contemporary Management

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Abstract

Primary thyroid lymphoma is an uncommon malignancy that constitutes fewer than 2% of all extranodal non-Hodgkin lymphomas (NHLs) and only 0.6% to 5% of all thyroid malignancies. Histologic subtypes include diffuse large B-cell lymphoma, mucosa-associated lymphoid tissue lymphomas, follicular lymphomas, and rarely Hodgkin lymphomas. The rarity of this disease precludes optimizing diagnostic and management modalities. This review provides an evaluation of the presentation of thyroid lymphoma and the current diagnosis, evaluation, and management of thyroid lymphoma.

Introduction

Primary thyroid lymphoma arises from the thyroid gland; the definition excludes malignancies originating from local invasion or distant metastasis. An uncommon malignancy, primary thyroid lymphoma constitutes fewer than 2% of all extranodal non-Hodgkin lymphomas (NHLs) [1] and only 0.6% to 5% of all thyroid malignancies [2]. Histologic subtypes include diffuse large B-cell lymphoma (DLBCL) (43% to 87% of cases), mucosa-associated lymphoid tissue (MALT) lymphomas (3% to 47%), follicular lymphomas, and other rare variants [2] (Table 1). Hodgkin thyroid lymphomas are relatively uncommon.

Historically, primary thyroid lymphoma was considered a surgical disease with the therapeutic goal of resection and debulking before adjuvant treatment (radiotherapy with or without chemotherapy) [3,4]. However, diagnostic tools — such as fine-needle cytology and axial imaging — now yield higher predictive values, so surgical management is rarely required.

In this article, our aim is to provide a comprehensive review of contemporary management of primary thyroid lymphoma.

Methods

A review of the literature was performed using Medline and Pubmed databases to identify all studies published up to February 2013 involving thyroid lymphoma. The MeSH search terms used were "thyroid lymphoma," "thyroidectomy," "surgery," "chemotherapy," "radiation therapy," and "chemoradiation therapy." The above terms and their combinations were also searched as text words. We excluded studies involving cancers of follicular and parafollicular origin, as well as poorly differentiated, advanced differentiated, and anaplastic thyroid cancer.

Results

Our search strategy yielded 35 studies related to the management of thyroid lymphoma and we included 35 studies that discussed the presentation, diagnosis, evaluation, and management of thyroid lymphoma.

Clinical presentation

Patients with primary thyroid lymphoma usually present with a rapidly enlarging neck mass [2]. The thyroid mass enlarges within 5 months (mean, 2.1 months) [5]. The mass is often firm; occasionally, it is fixed to adjacent structures [5]. Some patients have obstructive symptoms, including dyspnea, hoarseness, and dysphagia, though few patients (< 10%) report any pain or tenderness on palpation. Much less commonly, patients present with the so-called "B" symptoms of fever, night sweats, or weight loss (Table 2). Time interval from initial presentation to final diagnoses has not been reported.

Primary thyroid lymphoma is more prevalent in women, with a male:female ratio of 1:1.3 to 1:7.6. It most often presents in the 5th or 6th decade of life (Table 2). Few epidemiologic studies have described any racial prevalence, though a comprehensive study of prognostic factors in the United States conducted by Graff-Baker et al. found the highest prevalence in white populations [4]. In addition, Graff-Baker et al. found that, geographically, most patients with this disease are from the West (49%) and Midwest (28%).

Many epidemiologic studies of primary thyroid lymphoma have found an association with Hashimoto thyroiditis, with several patients presenting with either a past medical history or pathologic evidence of Hashimoto thyroiditis [1,2,5-8]. However, in a retrospective study of 24, 553 patients with Hashimoto thyroiditis in Japan, Watanabe et al. found that only 0.56% went on to develop primary thyroid lymphoma, with an incidence of 15.6 patients per 10,000 person-years [8].

Table 1: Frequency of Histologic Subtypes of Primary Thyroid Lymphoma.

Study (year)	Patients (n)	DLBCL	MALT-Lymphoma	DLBCL + MALT	Follicular lymphoma	Other*
Watanabe et al. [8]	171	43%	47%	8%	-	2%
Hwang et al. [5]	44	48%	39%	7%	-	6%
Graff-Baker et al. [4]	1408	70%	10%	-	10%	10%
Sun et al. [12]	40	72.5%	20%	-	-	7.5%
Katna et al. [1]	64	87.5%	3%	-	-	6%

**Includes small-lymphocytic and other non-Hodgkin variants. This table excludes Hodgkin lymphoma, which is rare (~2%).*
DLBCL: diffuse large-B-cell lymphoma
MALT: mucosa associated lymphoid tissue lymphoma

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Table 2: Clinical Presentation and Staging Frequency of Primary Thyroid Lymphoma.

Parameter	Derringer et al. [2]	Thieblemont et al. [6]	Ruggiero et al. [7]	Watanabe et al. [8]	Hwang et al. [5]	Graff Baker et al. [4]	Katna et al. [1]
Patients (n)	108	26	22	171	44	1,408	64
Mean age (years)	64.3	52	67.5	67	56.9	66.4	56
Sex (M:F)	1:2.7	1:7.6	1:2.7	1:4	1:4.5	1:3	1:1.3
Mass or nodule	28%	-	84%	-	-	-	87%
Rapidly enlarging mass	22%	87%	16%	30%	87%	-	-
Hypothyroidism	-	61%	-	36%	44%	-	-
Euthyroidism	-	33%	-	63%	53%	-	-
"B"symptoms	-	19%	-	5%	18%	13%	20%
Compressive symptoms	32%	-	60%	29%	18%	-	48%
Hashimoto thyroiditis	94%	31%	32%	90%	56%	-	14%
Stage*							
I	66%	54%	41%	29%	50%	56%	31%
II	25%	0%	18%	64%	30%	32%	36%
III	2%	0%	0%	3%	5%	2%	16%
IV	7%	46%	18%	4%	16%	11%	17%

**Staging criteria are based on the Ann Arbor Criteria, consistent with staging of other Hodgkin and non-Hodgkin lymphomas.*
"B" symptoms: fever, night sweats, or weight loss; compressive symptoms: dysphagia, cough, dyspnea, or hoarseness; F: female; M: male

Diagnostic considerations

The initial diagnostic workup for suspected primary thyroid lymphoma is similar to the workup for other rapidly enlarging goiters, including complete blood count (CBC), serum lactate dehydrogenase (LDH), serum beta$_2$-microglobulin, antithyroglobulin or antimicrosomal antibody, and thyroid function tests. The pattern of thyroid function associated with primary thyroid lymphoma is unclear, though 36% to 61% of patients may have hypothyroidism as measured by thyroid-stimulating hormone (TSH) levels greater than 4.5 IU/liter [6,8]. Only 1% to 6% of patients present with decreased TSH levels (< 0.1 IU/liter) [6,8]. The specific mechanism underlying the compromised thyroid function has not been elucidated; it may be associated with underlying Hashimoto thyroiditis or with replacement of thyroid parenchyma by the lymphomatous process.

Measurement of serum LDH and beta$_2$-microglobulincan also be helpful diagnostic indicators. However, only 23% to 47% of patients have elevated serum LDH levels [6,8], and only 24% have elevated serum beta$_2$-microglobulin levels [6]. The lack of sensitivity and specificity of the 2 tests excludes them from being diagnostic for primary thyroid lymphoma, though they may still be useful in explicating the clinical picture. Moreover, in a retrospective study of 26 patients, Thieblemont et al. found that elevated serum LDH and beta$_2$-microglobulin levels were associated with more DLBCL, suggesting that the 2 tests might be useful as a measure of disease aggression [6]. Serum LDH measurementas a prognostic indicator of response to treatment and of overall survival has been found to have no statistically significant value in multiple studies [1,5,9,10].

Fine-needle aspiration (FNA) has become the initial cytologic tool for diagnosing rapidly enlarging neck masses. In a clinicopathologic study and outcome analysis in 64 patients, Katna et al. found that, overall, FNA yielded a definitive diagnosis of primary thyroid lymphoma in only 28% of patients [1]. However, the yield has varied widely in other clinical studies: from 4% [3] to 90% [11]. Furthermore, thyroid lymphoma can be difficult to distinguish confidently from florid Hashimoto thyroiditis. Given the limitations of FNA, patients thought to possibly have thyroid lymphoma should undergo core needle biopsy, or, rarely, open biopsy. Hemithyroidectomy was performed diagnostically in 22-25% of primary thyroid lymphoma cases [3,12]. However, thyroid lobectomy or thyroidectomy is rarely indicated for diagnoses but may be appropriate under certain acute life-threatening circumstances [1,7,13,14]. It is unclear how many diagnoses of primary thyroid lymphoma are made incidentally in patients who receive thyroid surgery, as surgical intent is rarely reported. However, a case study of 17 primary thyroid lymphoma patients in Malaysia reported that in only 3 of 9 patients who underwent surgery was lymphoma unsuspected [13].

The advent of molecular techniques, such as immunohistologic staining and flow cytometry of biopsy samples, has allowed for greater diagnostic accuracy. Correctly identifying and differentiating histologic subtypes is imperative for assessing both ideal treatment options and prognosis. Molecular techniques help pinpoint immunoglobulin-specific binding to cell-surface markers and exploit differences in expression profiles. It is known that nearly all large B-cell lymphomas are CD19-, CD20-, and CD45- positive, whereas MALT lymphomas express surface immunoglobulin and are CD5-, CD10-, and CD23-negative [15]. Other useful markers such as Thryoglobulin, CD3, CD43, CD45RA, CD45RB, CD45RO, Bcl-2, Kappa r, and Lambda r have been described previously [2]. Assays may also be helpful in differentiating between Hashimoto thyroiditis and MALT lymphomas, which historically has been difficult to do by cytologic techniques alone, given lymphocytichomogeneity and small sample sizes [13,15]. The cytologic challenges of differentiating between Hashimoto thyroiditis and MALT lymphomas may be related to pathogenesis. Some authors have suggested that prolonged autoimmune antigenic stimulation may be responsible for the development of lymphocytic changes [5,16], and that underlying MALT lymphomas in patients with DLBCL may even imply a transformation from 1 subtype to the other [2].

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Gene expression profiling studies have enabled division of heterogeneous DLBCL into 2 major cell-of-origin phenotypes according to the classification method of Hans et al.: germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subgroups [17]. Prognostic differences between the 2 subgroups have been studied, with a relative consensus that a GCB diagnosis is associated with higher overall survival rates [1,8,16]. Yet in a retrospective univariate analysis of 37 patients, no single individual marker was associated witha significant prognostic difference [1].

Few clinical studies have assessed any genetic associations and/or mutations in patients with primary thyroid lymphoma. In a retrospective case series of 16 patients with DLBCL, 12 had an abnormal karyotype [16]. Of those 12 patients, 2 had t(8;14)(q24;q32) mutations, and 4 had 3q27 translocations [16]. Currently, the absence of a clear genetic pattern in patients with primary thyroid lymphoma makes genetic testing cost-ineffective and of little diagnostic value.

Imaging

The use of ultrasound has become routine in the assessment of thyroid masses. However, primary thyroid lymphoma lacks a unique appearance on ultrasound, so ultrasound in such patients is most effective when used in conjunction with a biopsy [18,19]. Ultrasound is in adequate in terms of primary thyroid lymphoma staging, which should be reserved for magnetic resonance imaging (MRI); if MRI is unavailable, then computed tomography (CT) should be used in order to sufficiently assess the presence and extent of extranodal involvement in the neck, mediastinum, and space below the diaphragm [18].

The use of ^{18}F-Flurodeoxygluoce positron emission tomography (FDG-PET) in staging and evaluation of response has been well established for a variety of malignancies [20]. Studies of PET imaging in primary thyroid lymphoma are currently limited but have shown some benefits in differentiating primary thyroid lymphoma from chronic thyroiditis [21] as well as advantages over CT imaging alone in assessing metabolic response and disease recurrence [22]. The relative paucity of data and potential utility of PET in managing patients with primary thyroid lymphoma necessitates further study.

Management

Monotherapy: The multiple histologic subtypes of primary thyroid lymphoma make uniform treatment impossible. Historically, surgery - total or subtotal thyroidectomy or partial thyroid lobectomy - was considered standard practice in the management of primary thyroid lymphoma [3,14]. The role of surgery, however, has been diminished, thanks to improvements in diagnosis and treatment [3,13].

Before the introduction of radiation therapy in the 1950s, surgical management alone for primary thyroid lymphoma conferred poor outcomes, with 5-year overall survival (5-year OS) rates of 20% [23]. The tendency was to attempt surgical resection whenever a tumor was small or confined to the thyroid; only when the lymphoma was of the inoperable extrathyroidal stage was radiotherapy alone resorted to [24].

The debate over the utility of surgery dates back to the 1970s. Devine et al. found that combining surgical resection with radiotherapy to treat lymphoma offered no significant survival advantage [24]. In contrast, Rossl et al. advocated total tumor excision, whenever possible, as well as postoperative radiation [25].

More recent retrospective case reports continue to muddy the waters, with 5-year overall survival rates ranging from 33% [26] to 100% [6]. In a case study of 6 patients with the MALT lymphoma subtype of primary thyroid lymphoma, Thieblemont et al. found that all 6 had acomplete response after surgery alone, with a 5-year overall survival rate of 100% [6]. However, it is well documented that MALT lymphomas patients have a better prognosis [1,2,4-6,8]: this early-stage subtype has an indolent course and reflects an "ideal scenario" applicable to only a small subset of patients whose outcomes should not be extrapolated to all patients with primary thyroid lymphoma.

Contemporary studies analyzing outcomes after surgery alone are scarce. Many institutions have accepted combined modality treatment as the mainstay, rightfully abandoning surgery alone. Future studies assessing treatment in patients with the low-grade, early-stage MALT lymphoma subtype may marshal evidence for the utility of surgery alone.

Radiation therapy alone has yielded a complete response in 67% to 97% of patients: the 5-year overall survival rates have ranged from 69% to 93%; the 5-year disease-free survival rates, from 63% to 78% (Table 3). Despite such favorable outcomes, Doria et al. reported an overall 37.1% relapse rate with radiation therapy alone [27], making the case for systemic therapy as an adjuvant to local treatment. Doria et al. did not assess specific radiation therapy dosing and protocols. One study recommends doses of 24 to 40Gy and clinical target volumes comprising the thyroid bed, bilateral cervical node levels 3, 4, and 6, and upper mediastinal lymph nodes [28].

Chemotherapy alone has yielded a complete response in 77% to 100% of patients: the 5-year overall survival rates have ranged from 55% to 60%; the 5-year disease-free survival rates, from 40% to 65%. All of the studies that we reviewed used CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like chemotherapy (CVP: cyclophosphamide, vincristine, prednisone) in either 3-dose or 6-dose regimens (Table 3), though the 3-dose regimen is considered standard practice [28].

The addition of rituximab, a chimeric anti-CD20 immunoglobulin G1 monoclonal antibody, to CHOP improved overall survival to 92%, as compared with 71% with CHOP alone (P=0.06) [29]. Few studies have assessed outcomes associated with the addition of rituximab to CHOP in patients with primary thyroid lymphoma specifically. Arguably, the therapeutic benefits of rituximab found in patients with other DLBCL lymphomas [30,31] can be applied to patients with DLBCL primary thyroid lymphoma as well, providing patients tolerate the adverse effects.

Combined Modality Treatment: According to retrospective case studies, the combination of radiation therapy and chemotherapy has yielded the most favorable outcomes, as compared with any single modality [1,7,14,27,29,32]. In a retrospective study of 87 patients, Onal et al. found a 5-year overall survival rate of 92% in such patients, as compared with only 61% in those treated with a single modality; the 5-year disease-free survival rate was also significantly higher in patients on both radiation therapy and chemotherapy (hazard ratio, 4.2;P= 0.03) [29].

In our review of the literature, we found a complete response in 85% to 92% of patients on both radiation therapy and chemotherapy: overall survival rates have ranged from 45% to 93%; the 5-year disease-free survival rates, from 77% to 93% (Table 3).

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Table 3: Treatment Outcomes of Stage IE and IIE Primary Thyroid Lymphoma

	Study	n	Complete response	5-year overall survival	5-year disease-free survival
Surgery	Vigliotti et al. [26]	3	-	33%	33%
	Thieblemont et al.[A] [6]	6	100%	100%	-
	Pyke et al. [33]	3	67%	-	-
Chemotherapy	Onal et al.[E] [29] CHOP +/- rituximab	21	-	57%	49%
	Mian et al.[C] [10] CHOP or CVP	13	77%	55%*	65%*
	Vigliotti et al. [26] CHOP +/- bleomycin	5	-	60%	40%
	Pyke et al. [33] CHOP	1	100%	-	-
Radiation therapy	Onal et al.[E] [29]	29	-	69%	63%
	Vigliotti et al. [26]	15	-	93%	78%
	Mian et al.[C] [10]	3	67%	-	-
	Laing et al.[D] [34]	39	97%	78%	67%
	Pyke et al. [33]	9	89%		
Chemotherapy + Radiation therapy	Onal et al.[E] [29] CHOP +/- rituximab	37	-	91%	91%
	Niitsu et al.[B] [16] CHOP	18	-	93%	93%
	Katna et al.[F] [1] CHOP +/- rituximab	28	85%	75%*	-
	Vigliotti et al. [26] CHOP +/- bleomycin	13	-	77%	77%
	Mian et al.[C] [10] CHOP or CVP	13	92%	45%*	84%*
Chemotherapy + Surgery	Mian et al.[C] [10] CHOP or CVP	7	72%	58%*	100%
	Pyke et al. [33] CHOP	3	67%	-	-
Radiation therapy + Surgery	Mian et al.[C] [10]	1	100%	-	-
	Thieblemont et al.[A] [6]	13	62%	44%	-
	Pyke et al. [33] doxorubicin	30	90%	-	-
Chemotherapy + Radiation therapy + Surgery	Mian et al.[C] [10] CHOP or CVP	11	100%	100%*	50%*
	Pyke et al. [33] CHOP	4	75%	-	-

Complete response, 5-year overall survival, and 5-year disease free survival criteria are consistent with those proposed by Cheeson et al. [35]
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: cyclophosphamide, vincristine, prednisone (used when doxorubicin contraindicated)

[A]MALToma patients only
[B]Stage I patients only
[C]DLBCL patients only
[D]MALT lymphoma patients only
[E]Onal et al.: 46 treated with CHOP, 14 with CHOP + rituximab, and 6 with other chemotherapeutic agents.
[F]Katna et al.: 22 treated with CHOP, 5 with CHOP + rituximab.
*Indicates extrapolated from Kaplan-Meier curve

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The combination of surgery and postoperative radiation therapy has yielded comparable complete response rates, but with a lower 5-year overall survival rate of 44% (Table 3).

The few studies that have assessed the efficacy of a combination of chemotherapy and surgery have reported complete response rates of 67% to 72% and a 5-year overall survival rates of 58% (Table 3), ruling this combined modality inappropriate for patients with primary thyroid lymphoma.

The current literature suggests that the combination of radiation therapy and chemotherapy is most appropriate for patients with primary thyroid lymphoma — a conclusion substantiated by the relative reduction in the relapse rate associated with this particular combined modality treatment [27]. In a series of 211 patients, Doria et al. found a relapse rate of only 7.7% in patients on both radiation therapy and chemotherapy, as compared with 37.1% with radiation therapy alone and 43% with chemotherapy alone [27].

In patients with primary thyroid lymphoma, the supplementation of surgery remains controversial. Pyke et al. reported no significant difference, either in the complete response rate or in the overall survival rate, between patients who underwent substantial debulking followed by adjuvant therapy versus patients with diagnostic biopsy results who underwent adjuvant therapy alone [33]. Likewise, Meyer-Rochow et al. reported no significant difference, in Kaplan-Meier disease-free survival curves, between patients who underwent thyroid resection versus patients with diagnostic open-biopsy results [3]. In contrast, Graff-Baker et al. reported data supporting an association between surgery and/or radiation and improved survival for patients with stage I MALT lymphomas, DLBCL, and small-lymphocytic variants per histologic tests [4].

Interestingly, Mian et al. found a clear trend, in the Kaplan-Meier curve, toward better overall survival in patients who first underwent surgical debulking followed by radiation therapy and chemotherapy [10].

Given the well-established operative risks (including recurrent laryngeal nerve palsy and hypoparathyroidism) associated with thyroid resection, surgery should be limited to patients who need an open biopsy after failure of diagnostic FNA and to those who need palliation of compressive symptoms [14]. 8-19% of patients treated surgically required tracheostomy for management of compressive airway symptoms or direct tracheal invasion [12,14,29].

Discussion

Asignificant limitation of our review is the inconsistency, due primarily to the subtypes of primary thyroid lymphoma, in the patient populations among the various studies. Very few of the studies we analyzed stratified outcomes by both histologic subtype and treatment modality [6,10,16,34] — a significant constraint, as different histologic subtypes may indicate different treatment modalities.

Many studies have reported a more favorable prognosis for MALT lymphoma patients than for DLBCL patients [1,2,4-6,8]. In the largest primary thyroid lymphoma study, to date (of 1,408 patients), Graff-Baker et al. found that the DLBCL subtype carried a 4.87-fold higher hazard ratio than the MALT lymphoma type [4]. Furthermore, Hwang et al. found a much higher complete response rate in MALT lymphoma patients (94%) than in DLBCL patients (53%) ($P < 0.01$) [5]. These findings support the utility of an accurate histologic diagnosis and the need for future studies assessing outcomes by histologic subtype.

Another limitation of our review is the prevailing lack of consensus regarding chemotherapeutic agents and radiation techniques. Most studies used CHOP or CHOP-like regimens, but outcomes may have been distorted by the addition of rituximab or bleomycin and by the use of other modalities such as CVP [1,10,16,26,29,33]. Radiation therapy also varied in terms of exposure fields, dosage, and frequency, possibly sullying interpretation of outcomes [1,6,10,16,26,29,33,34].

Conclusion

Lymphoma arising primarily from the thyroid gland is rare. The rarity of thyroid lymphoma precludes the implementation of prospective randomized trials to determine the optimal treatment modality. However, with the limited data available, multimodality treatment provides the best opportunity to achieve increased survival.

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