Management for primary thyroid lymphoma: Experience from a single tertiary care centre in Taiwan

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Abstract
Background: Diverse treatments are available for different histological types of thyroid lymphoma: concurrent chemoradiotherapy for diffuse large B cell lymphoma (DLBCL) and radiotherapy or thyroidectomy for low-grade mucosa-associated lymphoid tissue (MALT) lymphoma. However, diagnosing lymphomas before operation is difficult, because the diagnostic yield of fine-needle biopsies is limited by the rarity of the disease. Therefore, patients may undergo unnecessary thyroidectomies.

Purpose: To investigate the efficacy of various biopsy procedures and explore indications for thyroidectomy in patients with primary thyroid lymphomas.

Methods: The demographics, types of biopsy procedures, treatments, and outcome data of patients diagnosed with primary thyroid lymphoma at Tri-Service General Hospital between 1992 and 2015 were retrospectively collected.

Results: Ten patients received a diagnosis of primary thyroid lymphomas; eight with DLBCL and two with MALT lymphoma. None of these patients received a definitive diagnosis after fine-needle aspiration biopsies; however, six patients received their diagnosis and histological-subtype classification after core-needle biopsies. Before 2004, three patients with DLBCL underwent thyroidectomies for diagnostic purposes and one encountered vocal cord palsy. By contrast, two patients with localized MALT lymphoma underwent thyroidectomies for treatment, with both experiencing favorable outcomes and prognoses.

Conflicts of interest: The authors declare no conflicts of interest.

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1. Introduction

Primary thyroid lymphoma is rare, accounting for <5% of thyroid malignancies. The two distinct histological types of primary thyroid lymphoma are diffuse large B cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma. Because DLBCL is sensitive to chemotherapy and radiotherapy, the general consensus is to avoid extensive surgery. By contrast, radiotherapy or thyroidectomy is typically used as the initial treatment for localized MALT lymphoma. Fine-needle aspiration cytology, the most common initial diagnostic tool used in thyroid malignancies, is difficult to use for diagnosing tumor type, which is necessary for treatment planning. However, core-needle biopsy, which is less commonly used in thyroid-gland biopsies, may serve as a substitute to surgical biopsy. This study investigated the efficacy of various biopsy procedures, and explored indications for thyroidectomy in patients with primary thyroid lymphoma.

2. Methods

We retrospectively surveyed patients diagnosed with primary thyroid lymphoma at Tri-Service General Hospital between 1992 and 2015. After receiving approval from the hospital Institutional Review Board (TSGHIRB: 2-102-05-108), we collected patient data from medical charts and the cancer registry database of our hospital. This information included sex, age at disease onset, history of thyroiditis, presence of significant airway compression, goiter size, lymph node involvement, types of biopsy procedures, stage of disease, modalities of treatment, major complications related to treatment, duration of follow-up, and recurrences. The tumor size and extent of involvement were assessed through computed tomography (CT). Ultrasound-guided core-needle biopsies were performed by radiologists. The extent of thyroid operations varied from lobectomy to total thyroidectomy. Pathological diagnoses were made by two pathologists who utilized both hematoxylin and eosin, as well as immunohistochemistry staining to differentiate lymphoma subtypes from Hashimoto’s thyroiditis. The staging investigation included blood counts, blood chemistry, chest and abdominal CT, and bone marrow biopsies. Additionally, whole-body gallium scans, whole-body bone scans, or whole-body positron emission tomography (PET)/CT was performed in some patients. Disease stage was classified according to the Ann Arbor staging system: diseases confined to the thyroid gland were classified as stage IE, and those with regional node involvement were classified as stage IIE. The final follow-up was conducted until October 31, 2015.

3. Results

Ten patients with primary thyroid lymphoma were identified. Of these, eight had DLBCL, and two had MALT lymphoma. Patient demographics, pathological diagnoses, and disease stages are listed in Table 1. In total, six women and four men were identified. The mean age at onset was 67.9 years (range, 54–83 years). All patients developed rapidly growing neck masses over months, with mean tumor size of 7.1 cm (range, 3.8–11.4 cm).

Nine patients underwent fine-needle aspiration biopsy (FNAB); of these, no patient received a definitive diagnosis. Four patients received a definitive diagnosis only after thyroidectomy. Of these four patients, three were diagnosed with DLBCL and one with MALT lymphoma. After 2004, core-needle biopsy was performed in selected cases, with six patients undergoing the procedure. Of these, five received a final diagnosis of DLBCL and one of suspected low-grade lymphoma, which was confirmed as MALT lymphoma through thyroidectomy. No complications were observed after both fine-needle and core-needle biopsies. One patient with DLBCL had vocal cord palsy after subtotal thyroidectomy for the initial diagnostic purpose.

Table 2 lists treatment types, major treatment-related complications, initial disease stages, and their corresponding outcomes. All patients with DLBCL underwent chemotherapy with a platinum-based regimen. Three patients also received adjuvant radiotherapy. Two patients with MALT lymphoma underwent thyroidectomy as the primary treatment. Patient five initially underwent a lobectomy, after which the frozen tissue section indicated benign disease, and he had subsequent completion of a thyroidectomy and adjuvant radiotherapy, because the final pathological assessment revealed Hashimoto’s thyroiditis with marginal cell lymphoma (MALT lymphoma). Patient 8 underwent subtotal thyroidectomy. Neither Patient 5 nor Patient 8 underwent chemotherapy.

The mean follow-up period was 58.1 months (range, 5–123 months). Two patients with DLBCL developed recurrence. Patient 2 experienced regional recurrence along with airway compression and tracheocutaneous fistula 10 months after the operation. The patient was treated with salvage chemotherapy, with four cycles of EPOCH regimen (VP-16 + vincristine + adriamycin + methylprednisolone + cyclophosphamide) and radiotherapy, subsequently resulting in
complete remission. Patient 4 experienced regional recurrence, causing acute respiratory failure 46 months after operation. Pulse-steroid therapy and further radiotherapy (4500 cGy in total) achieved complete remission. One patient died from an unrelated medical cause. One patient with DLBCL experienced partial remission after eight cycles of the R-CHOP regimen; however, the patient died from sepsis during salvage chemotherapy.

In Patients 4, 6, 7, and 10 with DLBCL, systemic steroid therapy immediately relieved airway compression and precluding the need for tracheostomy. Additionally, remarkable tumor shrinkage was observed after chemotherapy. A comparison of the neck CT scans of Patient 6 before and after treatment is presented in Figure 1.

4. Discussion

Primary thyroid lymphoma is rare, accounting for only 5% of thyroid malignancies and 2% of extranodal lymphomas. Thyroid lymphoma typically presents as a rapidly growing neck mass that is sometimes accompanied by respiratory compression symptoms. Thyroid lymphoma is more predominant in women and has a peak onset age of 50 to 70 years.2–4 The risk of thyroid lymphoma is high in individuals with a history of chronic thyroiditis, such as Hashimoto’s thyroiditis.5,6 Similar to other lymphomas, subtypes in thyroid lymphoma are classified according to histological and immunological features. B cell non-Hodgkin’s lymphoma is the most common subtype, whereas DLBCL and marginal-zone B cell lymphoma of MALT type (MALT lymphoma) are other common subtypes that may also co-occur in a single patient.7 Follicular, small lymphocytic, and T cell-origin lymphoma are other less common subtypes of the disease. Ultrasound is a common diagnostic tool for measuring the thyroid mass, because it reveals hypoechoic masses intermingled with echogenic structures and enhances posterior echoes.7 FNAB is often used as an initial tool for the pathological diagnosis of the thyroid nodule and can provide a suggestive diagnosis.
of lymphomas. Microscopically, large-cell lymphomas are observed as atypical large lymphocytes with frequent mitosis and reveal positive B cell markers (CD20 and CD79a) on immunohistochemical staining. By contrast, low-grade lymphomas are observed as a mixture of small and large lymphocytes, mimicking Hashimoto’s thyroiditis. In uncertain diagnoses, adjuvant tests, such as immunophenotyping, flow cytometry, and polymerase chain reaction-based detection of the immunoglobulin heavy chain gene, may be helpful; however, because of the rarity of the disease, availability of these adjuvant tests varies among institutions, and no universal standard is available.

Accordingly, false-negative results have limited diagnostic accuracy to 59% to 88%. FNAB failed to diagnose thyroid lymphoma in all nine patients examined in the current study. This is likely attributable to the inadequate experience of our cytopathologists resulting from the rarity of the disease, and we believe most clinicians in low-volume centers may face similar dilemmas.

In this study, all patients received a final diagnosis after a core-needle biopsy or thyroidectomy. Biopsy procedures performed to obtain an adequate specimen remain necessary for our pathologists to differentiate the histological subtypes of thyroid lymphoma. Five of our patients were diagnosed using ultrasound-guided core-needle biopsies, avoiding the need of further surgery for diagnosis. Ultrasound imaging is a valuable tool, because it can identify solid tumor lesions while avoiding necrotic lesions or vessel injuries. In all thyroid malignancies, the accuracy obtained using core-needle biopsy was higher (up to 92.1%) than that obtained using FNAB. Histological sub-classification is possible, because core-needle biopsy successfully subclassifies histological types in 89.7% of neck lymphomas. This technique provides an adequate amount of specimen for the detection of prognostic markers, such as Ki-67 and p53, through immunohistochemistry staining, enabling a reliable differentiation between Hashimoto’s thyroiditis and anaplastic carcinoma. Considering the indeterminate results of FNAB, core-needle biopsy can be used as a complementary diagnostic tool before surgery.

In core-needle biopsy, bleeding is a major concern; however, no bleeding complication related to needle biopsy was observed in this study. Studies reported the incidence of hematoma formation as being slightly higher after core-needle biopsy (0.02–2.00%) as compared with that observed after fine-needle biopsy; however, none of the patients required hospitalization. Additionally, while the ultrasound-guided core-needle biopsy typically requires fewer needle passes as compared with those required for fine-needle biopsy, the adequacy of the specimen is superior. Therefore, ultrasound-guided core biopsy is an efficient and relatively safe alternative to open biopsy for the diagnosis of thyroid lymphoma.

The proposed management algorithm for primary thyroid lymphoma is presented in Figure 2. In patients with rapidly growing neck masses and a diffuse infiltrative image pattern, the differential diagnosis may include anaplastic carcinoma, poorly differentiated thyroid cancer, and thyroid lymphoma. Once initial FNAB fails to definitively diagnose the tumor type, core-needle biopsy should be
considered. In patients with a diffuse infiltrative image pattern or high clinical suspicion of lymphoma, core-needle biopsy may be used instead of FNAB as an initial diagnostic test. For example, Patient 7 underwent core-needle biopsy without undergoing a prior FNAB. The results of the biopsy revealed DLBCL, precluding the need for any additional surgical biopsy.

The staging work-up involves physical examination, laboratory blood tests (complete blood counts and biochemistry data, including beta-microglobulin and lactate dehydrogenase values), radiological imaging (CT/magnetic resonance imaging (MRI) scans and MRI), nuclear medicine imaging (gallium scan and PET scans), and bone-marrow examination. CT or MRI scans are valuable in defining the local extent of the disease, such as a potential extrathyroid invasion, substernal extension, and lymph node involvement. In patients suitable for thyroidectomy, resectability is also ideally evaluated through CT scans to assess vascular enhancement or prevertebral fascia invasion; however, nuclear imaging is more useful for evaluating the extent of lymph node involvement and distant metastasis. PET-CT scans largely replaced gallium scans at our institute after 2008, because they provide more precise localization and provide high sensitivity and specificity for all lymphoma subtypes, especially those of an indolent nature (such as MALT and follicular). Compared with nodal non-Hodgkin’s lymphomas, primary thyroid lymphoma tends to be less invasive. Most cases of thyroid lymphoma belong to Ann Arbor stage IE or IIE. The prognosis is poor for patients with an International Prognostic Index score ≥2 (including advanced stage and age), large B cell or follicular histology, or inadequate local tumor control by radiation or surgery. Additionally, the histological findings of vascular invasion, abundant apoptosis, high mitotic rate, and perithyroidal soft-tissue invasion are associated with poor prognosis.

Figure 2. The proposed management algorithm for primary thyroid lymphoma. DTC = differentiated thyroid cancer; PDTC = poorly differentiated thyroid cancer; DLBCL = diffuse large B cell lymphoma; MALT = mucosa-associated lymphoid tissue.
Conducting prospective, randomized trials is difficult due to the limited number of cases. Therefore, a single standard treatment is not available for thyroid lymphoma. Common treatment regimens are derived from the treatment of extranodal lymphomas. Thyroidectomy and radiotherapy are effective for local tumor control; however, chemotherapy is necessary in aggressive, disseminated disease. In both retrospective studies of thyroid lymphoma and prospective studies of extranodal lymphoma, more favorable survival was achieved through combined radiotherapy than through a single treatment. However, a limitation of these studies is the lack of differentiation among histological subtypes of thyroid lymphoma. DLBCL usually presents as a more aggressive and disseminated disease, whereas MALT lymphoma tends to be localized. Localized treatment through surgery or radiotherapy produces satisfactory results for early-stage MALT lymphoma. Radiotherapy alone can deliver excellent long-term relapse-free survival in stage I and II thyroid MALT lymphoma. Moreover, no clear survival benefit is yielded when chemotherapy is used for MALT lymphoma. The outcomes of large cells or high-grade malignant cells admixed with MALT lymphoma are similar to or poorer than those of pure diffuse large-cell-subtype lymphoma. In such cases, a more aggressive treatment should be used. The complete surgical resection of the thyroid can exclude this possibility. In Patient 5, total thyroidectomy was performed despite a previous pathological diagnosis of MALT lymphoma. The reasons for removing the remaining thyroid tissue were both to establish a definitive diagnosis and to cure the localized lymphoma. Because high-grade malignancies were excluded by pathology, the patient underwent adjuvant radiotherapy instead of chemotherapy. No recurrence was observed after 107 months of follow-up, consistent with favorable outcomes expected from surgical treatments of MALT lymphoma.

From our experiences of surgeries involving thyroid lymphoma, we suggest thyroidectomy in localized, stage I or II MALT lymphoma, but not in any stage of DLBCL, because the infiltrative nature of large B cell lymphoma puts the recurrent laryngeal nerve at risk. Because determining histological subtypes is useful for treatment planning, effective biopsy is crucial. Additionally, CT should be performed before operation in patients requiring thyroidectomy in order to evaluate resectability.

The airway obstruction caused by thyroid lymphomas requires urgent treatment. Endotracheal-tube insertion or tracheostomy is the first step to securing the airway in an emergency situation, followed by definitive treatment. Radiotherapy alone with pulse-steroid therapy can induce tumor necrosis and shrinkage. Once DLBCL is confirmed by biopsy, airway compression can be further relieved using a combination of steroid, chemotherapy, and radiotherapy. Thyroidectomy may also have an immediate relieving effect on the airway obstruction, however, complete resection is usually impossible due to the infiltrating tumor or extensive growth, posing a high risk of injury to the recurrent laryngeal nerve or parathyroid glands.

Our experience suggests that effective biopsy is necessary for the accurate histological diagnosis of thyroid lymphomas. In addition to surgical biopsy, ultrasound-guided core-needle biopsy is a safe and effective alternative. When DLBCL is confirmed, the treatment of choice should be combined chemoradiation instead of extensive surgery. By contrast, MALT lymphoma tends to be localized and could be treated using radiotherapy. Thyroidectomy may be considered in resectable cases to exclude large-cell transformation, which requires chemotherapy and worsens outcomes. Consequently, the need for surgical treatment in patients with primary thyroid lymphomas should depend on the histological subtype and disease stage.

References


