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Original Article

Outcomes of Primary Thyroid non-Hodgkin's Lymphoma

A Series of Nine Consecutive Cases

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Abstract

Primary non-Hodgkin's lymphoma (NHL) of the thyroid gland is a rare disease with an incidence of 0.5 per 100,000 population. Stages IE and IIE thyroid NHL have been traditionally treated by surgical resection; however, modern treatment consists of chemotherapy and local radiotherapy, and surgery is often reserved for tissue diagnosis and relief of airway compression. We retrospectively reviewed the management and outcomes of nine consecutive patients with thyroid NHL, eight females and one male (median age 63 yr, range 34–71 yr) treated between 1994 and 1999. Five patients had disease stage IE and 4 stage IIE. Median follow-up was 72 mo. Pathohistology and immunohistochemistry identified two patients with mucosa-associated lymphoid tissue (MALT), three follicular center cell lymphoma (FCC), two patients large B-cell lymphoma (BLCL), one a marginal zone lymphoma (MZL), and one patient a peripheral T-cell lymphoma (PTCL). Total thyroidectomy was performed in three patients and subtotal thyroidectomy in four. One (MALT) patient underwent surgery alone; three patients surgery, radiotherapy, and chemotherapy (two FCC, one PTCL); three patients surgery and chemotherapy (one MALT, one FCC, one LBCL); and two chemotherapy alone (one LBCL, one MZL). Median survival was 79 mo (range 13–124 mo). The PTCL patient, a 34-yr-old man, died from disseminated disease at 13 mo despite secondary chemotherapy, and one LBCL patient with extensively invasive local disease died from stroke 17 mo after diagnosis. The remaining seven patients remain in remission with no local or systemic relapse at a mean of 86 mo. With appropriate therapy primary thyroid NHL has a favorable course; however, prognosis depends on the histology, local spread, and the stage of the disease at presentation, as well as the patient's performance status. Surgery in combination with chemotherapy and/or radiotherapy is still warranted for intermediate and high-grade thyroid NHLs, with over 77% of patients achieving long-term remission. Peripheral T-cell lymphoma carries a poor prognosis.

Key Words: Non-Hodgkin's lymphoma; thyroid gland; thyroidectomy; radiotherapy; chemotherapy.

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Introduction

Primary lymphomas of the thyroid gland are rare, with an incidence of 0.5 per 100,000 population, and account for 2.5–3% of all non-Hodgkin's lymphomas (NHL) and 5% of all thyroid malignancy *(1).* Women are more commonly affected with a median age at presentation of over 60 yr *(1)* and 80% present in disease stage I or II. NHLs of the thyroid are predominantly B-cell tumors *(2–14),* although T-cell thyroid lymphomas often appear in the Japanese literature *(15).* Their association with pre-existing chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) is also well established *(3,7,15).* Patients usually present with a palpable nodal mass in the thyroid or with a rapidly enlarging neck mass causing local obstruction and infiltrative symptoms in the more aggressive disease forms; in these cases the tumor is often bulky and neck lymphadenopathy is frequently present.

In the past surgery was often performed because of the inability to preoperatively distinguish lymphoma from carcinoma or thyroiditis. Surgery is now more commonly limited to obtaining pathological specimens by biopsy or fine-needle aspiration, definitive treatment being chemotherapy with or without radiotherapy. However, those patients who have had complete resection of the lymphoma often still run a better course than those without resection, and thus surgery continues to play an important role.

Patients and Methods

Between 1994 and 1999, 423 patients with stages I and II NHL were referred to our unit. These included nine patients (eight female, one male) with primary thyroid NHL, with a median age at presentation of 63 yr (range 34–71 yr). Six patients presented with an enlarged thyroid mass in one lobe (of 1–10 wk of duration), one patient had diffuse enlargement of the neck, and two patients had a single nodal mass in the thyroid gland, neck lymphadenopathy, and multinodular goiters. Dyspnea was present in three patients, dysphagia in one, stridor in one, and hoarseness in three.

Each patient was thoroughly examined and investigated with laboratory studies, chest X-ray, abdominal and cervical ultrasound scan, abdominal and cervical CT scanning, bone marrow aspiration, and histology. Two patients also underwent lymphangiography. Five patients underwent fine-needle-aspiration biopsy (FNAB), although thyroid NHL was only diagnosed in two of the samples, with one sample being non-diagnostic and pathologist uncertainty clouding the remaining two specimens. Thus, seven of the nine patients had diagnoses established following more extensive surgery. Of those operated, four patients underwent subtotal thyroidectomy and three total thyroidectomy with regional lymph node dissection.

Five patients were staged as IE and four as stage IIE according to Ann Arbor Staging Classification. Clinical and pathologic data of the nine patients are summarized in Table 1. Median follow-up was 72 mo.

Histology and Immunophenotyping

All patients had immunohistochemical studies performed using paraffin sections and the avidin–biotin peroxidase complex technique with a panel of monoclonal antibodies. Of these nine primary thyroid NHLs, two were mucosa-associated lymphoid tissue (MALT) lymphomas (with the immunophenotype CD5–, CD10–, CD11c+, CD20+, CD79α+, CD23–, CD43+/–, SIgM+), two were large B-cell lymphomas (LBCL) (immunophenotype CD20+, CD22+, CD79α+ with large-cell morphology), three were follicular centre cell lymphomas (FCC) with a diffuse growth pattern of small cells (FCC-intermediate grade risk which were CD5– and CD43–, CD10+, CD20+, and CD79α+ and strongly BCL-2++), one patient had a marginal zone lymphoma (Figs. 1 and 2) and one patient had peripheral-T-cell lymphoma (CD3+, CD5+, CD7–, CD43+, CD45RO+, CD20–, CD79α–, EMA–, HTLV-1 negative) (Fig. 3), characterized by a proliferation of small to large lymphoid cells with irregular nuclei.

In four patients the lymphoma was associated with Hashimoto's thyroiditis; one of these patients (patient 4) also had a diffuse sclerosing papillary carcinoma of the thyroid gland (Figs. 4 and 5). In one patient (patient 3) the LBCL had extensively infiltrated the surrounding tissues (trachea, esophagus, carotid artery, jugular vein, and recurrent laryngeal nerve), while another patient with LBCL (patient 8) had involvement of the surrounding lymph nodes and had had preceding hypothyroidism and a goiter.

Table 1
Clinical and Pathology Data of the Nine Patients with NHL of the Thyroid Gland

No.	Age/sex	Stage	Histology B-cell / T-cell	Hashimoto's thyroiditis	Surgical therapy	Chemotherapy	Radiotherapy
1	67 / F	II E "A"	FCC / B	No	Subtotal thyroidectomy	COP, 6 courses	40 Gy locoregional
2	63 / F	II E "A"	LCL / B	No	Subtotal thyroidectomy with neck dissection	Chlorambucil Prednisolone	No
3	64 / F	II E "B"	FCC / B	Yes	Subtotal thyroidectomy	COP 6 courses	44 Gy
4	64 / F	I E	FCC / B DSPC	Yes	Total thyroidectomy with neck dissection	CHOP 6 courses	No
5	62 / F	I E	MALT	No	Total thyroidectomy	No	No
6	62 / F	I E	MALT	No	Total thyroidectomy with neck dissection	CHOP 2 courses	No
7	34 / M	I E	Peripheral T-cell	No	Subtotal hemithyroidectomy	CHOP 6 courses ProMACE CytaBOM 6 courses	44 Gy
8	42 / F	II E	LCL / B	Yes	FNAB	CHOP 6 courses	No
9	71 / F	I E	Marginal zone lymphoma	Yes	FNAB	CHOP 6 courses	No

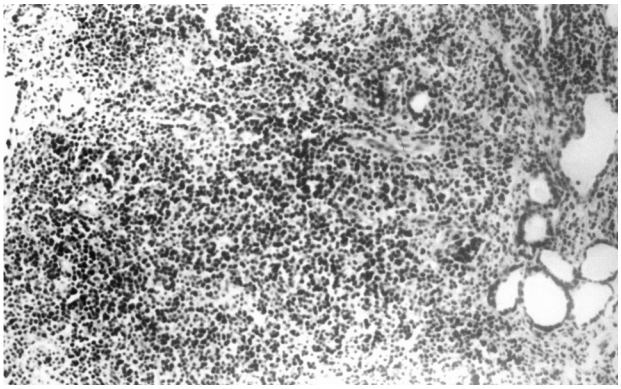

Fig. 1. Marginal zone B cell lymphoma (MALT) involving thyroid gland (H&E, × 100).

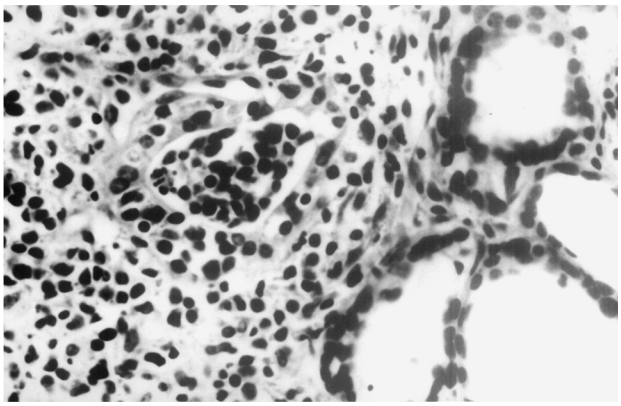

Fig. 2. MALT lymphoma with admixture of small lymphocytes, monocytoid B cells, centrocyte-like cells and occasional large cells showing infiltration of thyroid follicle, forming "lymphoepithelial lesion" (H&E, × 400).

Treatment and Results

Patients underwent surgery alone or with adjuvant chemotherapy and/or radiotherapy, or were treated with chemotherapy alone, at a mean of 3 wk after initial presentation. One patient (patient 6) with stage IE MALT lymphoma received two cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy following her total thyroidectomy and neck dissection,

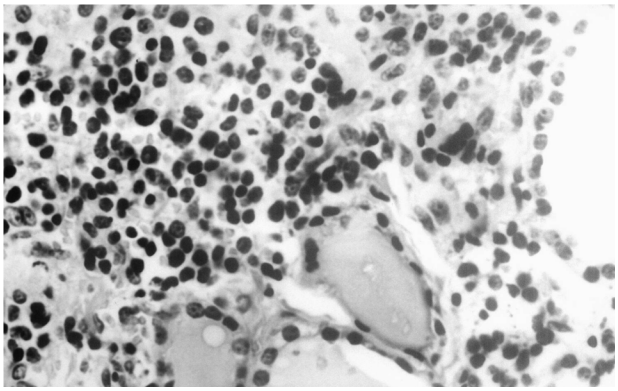

Fig. 3. Peripheral T cell lymphoma of the thyroid gland showing irregular lymphocytes of various sizes and few histiocytes (H&E, × 400).

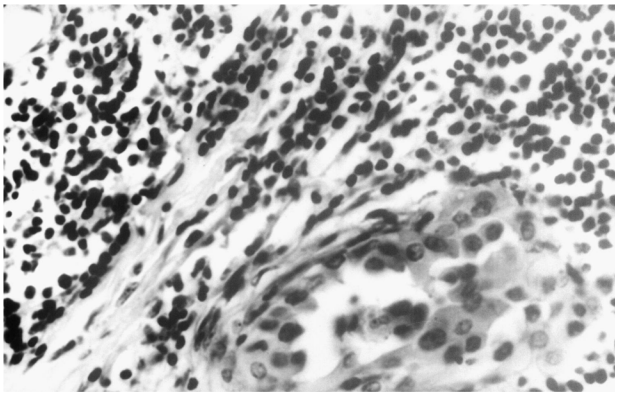

Fig. 4. Island of papillary carcinoma with vesicular "Orphan Annie" nuclei surrounded by diffuse follicle center lymphoma consists of small irregular lymphocytes with few large cells (H&E, × 400).

and remains in complete remission after 6 yr and 5 mo. A second patient (patient 5) with MALT lymphoma refused adjuvant therapy following her total thyroidectomy and remains in complete remission at 3 yr and 5 mo. Two patients (patients 1 and 3) with FCC lymphoma underwent subtotal thyroidectomy, chemotherapy (COP protocol: cyclophosphamide, vincristine and prednisone), and locoregional radiotherapy, with 40 and 44 Gy, and remain in remission at 10 yr 2 mo and 8 yr 9 mo, respectively, while the third patient (patient 4) with FCC lymphoma had a total thyroidectomy and neck dissection followed by six courses of CHOP protocol chemotherapy, and remains in remission at 8 yr

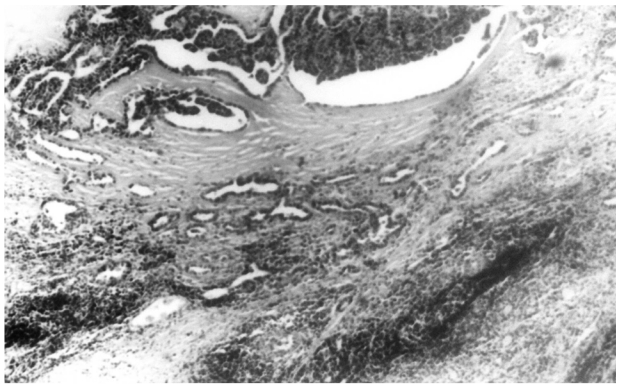

Fig. 5. Papillary carcinoma and lymphoma of the thyroid gland (H&E, × 40).

six mo. One patient (patient 7) with peripheral T-cell lymphoma received six courses of CHOP and local radiotherapy with 44 Gy, following a subtotal thyroidectomy; however, developed a systemic relapse involving the remaining thyroid gland, lungs, skin, and central nervous system (CNS) 2 mo after completion of adjuvant treatment. This relapse was treated according to the chemotherapeutic ProMACE-CytaBOM protocol (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytosine arabinoside, vincristine, and bleomycin). The patient initially showed some signs of improvement after four cycles; however, the patient died from disseminated disease 13 mo from first diagnosis.

One patient (patient 2) with LBCL received chlorambucil and prednisolone therapy following a subtotal thyroidectomy. This patient never achieved remission, owing to extensive local disease invasion, and she died of a stroke 17 mo after initial diagnosis. The second patient (patient 8) with LBCL and the patient with marginal zone lymphoma (patient 9) were treated with chemotherapy alone (six cycles of CHOP protocol), following FNAB, and remain in remission at 6 yr 3 mo and 6 yr 7 mo, respectively.

All three patients receiving radiotherapy (patients 1,3, and 7) complained of self-limiting pharyngitis and/or esophagitis during and after their treatment. Two patients in whom total thyroidectomy (patients 5 and 6) was performed developed hypothyroidism, requiring thyroxine treatment.

Discussion

The clinical features of thyroid NHL are often fairly nonspecific and include dyspnea, dysphagia, stridor, and hoarseness related to local compression and infiltration by the tumor masses *(7–14).* As they occur fairly rarely, the diagnosis is often overlooked, and thyroid NHL is frequently treated as thyroid carcinoma *(1,7,8).* However, thyroid NHL should always be suspected in elderly patients, especially women in their sixties or seventies, with a rapidly enlarging painless thyroid mass *(3,6,16–20).*

Immunohistochemistry and the identification of tumor cell lineages with monoclonal antibodies have increased the diagnostic potential of FNAB, and this is an appropriate diagnostic method in those patients who have not had previous Hashimoto thyroiditis. However, it can be difficult to distinguish lymphoma of the thyroid from a poorly differentiated thyroid carcinoma or Hashimoto's thyroiditis *(5–7)* on the basis of cytology alone, as we have seen in our series. Thus, when there is a high index of suspicion for thyroid NHL, and especially Hodgkin's lymphoma, many surgeons prefer to proceed to an incisional biopsy with intraoperative frozen section pathological evaluation *(3,6).*

Most thyroid lymphomas reported in the literature have a diffuse large B-cell histology *(1,3,10,11),* although some authors have found that the majority are of the MALT-type; we found equal numbers of each in our case series. These differences in the frequency of histological subtypes of thyroid NHL in reported series may be the result of transformation during the course of MALT lymphomas into more aggressive tumors such as the diffuse LBCL *(12).*

The role of surgery for thyroid NHL in stages IE and IIE is still unclear, as survival rates do not seem to be improved when radical surgery is added to other treatment modalities *(1).* Tupchong et al. *(14)* performed primary radical surgery for local tumor control in their lymphoma patients, but found no statistically significant differences in survival rates between patients who underwent lobectomy, subtotal, or total thyroidectomy *(14).* Our experience supports the use of surgery in the initial phase of treatment, based on the long survival of those patients who underwent subtotal or total thyroidectomy, in conjunction with adjuvant chemotherapy and/or radiotherapy. Indeed one patient (patient 5) with a MALT tumor remains well 41 mo after undergoing total thyroidectomy alone.

Radiotherapy alone or in combination with surgery may be appropriate in patients with low-grade small-bulk malignancy confined to the thyroid gland *(2,14–18),* where locoregional moderate-dose radiation (35–45 Gy) achieves control in more than 75% of patients. However, relapse can occur outside the radiation field owing to the existence of residual disease, and although local relapse is uncommon, systemic progression after radiation of the GI tract and Waldeyer's ring can occur in patients with MALT NHL *(1).* Thus, radiotherapy in combination with chemotherapy or with surgery is recommended to achieve long remission without local or systemic relapse *(3,12,14).*

A review by Doria et al. in 211 patients in 11 series *(3)* showed systemic relapse of disease does not occur in MALT lymphomas alone, but also in other histological subtypes *(3,6),* and so advocate the use of combined-modality therapy, e.g., chemotherapy and local radiotherapy even in stages I and II of all disease subtypes *(6).*

Some series have reported that almost all their patients had Hashimoto's thyroiditis *(7,15,16).* Hashimoto's thyroiditis, an autoimmune condition, is thought to lead to a chronic proliferation of lymphoid tissue, which after mutation and clonal expansion can lead to the development of NHL *(21).* We had four such patients, one of whom (patient 4) had a concomitant diffuse sclerosing papillary carcinoma of the thyroid. After a total thyroidectomy, neck dissection, and chemotherapy, she remains in complete remission 8 yr 6 mo from initial diagnosis.

Outcomes of thyroid NHL depend on the stage of disease, infiltration of local organs, histology, and patient's performance status; treatment combinations should be tailored to each individual patient with adjustment for these prognostic factors *(3,6).* The overall survival rates at 5 and 10 yr are 90% for patients with MALT-type NHL, compared with 55% at 5 yr for patients without evidence of MALT *(3,6,12).* Survival in our cohort of patients was comparable to that reported for groups of patients managed with combined-treatment modalities, with median survival of 79 mo (mean 86 mo). The worst prognosis appeared to be in our only male patient, a young man with peripheral T-cell lymphoma

(patient 7), who relapsed after treatment by subtotal thyroidectomy, chemotherapy, and locoregional radiotherapy. His systemic relapse within the first year reflects the greater severity of T-cell lymphomas and its dissemination despite the use of combination therapy. The presence of stridor, secondary to tumor bulk, may also be a negative prognostic factor. We observed stridor in only one patient (patient 2), and despite undergoing a subtotal thyroidectomy and chemotherapy she died of a stroke 17 mo later.

Thus it appears that at present there is no panacea for the treatment of thyroid NHL; however, with the development of new chemotherapeutic drugs and genetically engineered therapies, in combination with surgery, one expects survival rates to continue to increase, even in the more aggressive and recurrent disease *(22)*.

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