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☐Original Article☐

Primary Lymphoma of the Thyroid

Jee Sook Hahn[1], Hyun Cheol Chung[1], Yoo Hong Min[1], Yun Woong Ko[1] Cheong Soo Park[2], Chang Ok Suh[3], Gwi Eon Kim[3] and Woo Ick Yang[4]

Primary lymphoma presenting in the thyroid gland is uncommon. A review of the Yonsei University Medical Center experience between 1982 and 1994 was performed retrospectively to assess the treatment outcome and prognostic factors. There were four females and one male, and the median age was 65 years. All 5 cases presented with a neck mass. Two of them had co-existing biopsy-proved Hashimoto's thyroiditis and three cases were each in a hypothyroid state. All cases with non-Hodgkin's disease were of intermediate grade. One case was in stage IE and four were in stage IIE. Three cases were treated with surgery alone and two cases with bulky inoperable stage IIB were treated with chemo-radiotherapy. Chemotherapy induced a complete response in one and a partial response in the other with minimal transient toxicity. As the questions regarding justification for extensive surgical intervention increase, combined chemo-radiotherapy can be suggested as an initial treatment even in stage I, and stage II thyroid lymphoma based on prognostic factor evaluation.

Key Words: Thyroid, lymphoma, chemo-radiotherapy

Primary thyroid lymphoma is an uncommon disease, comprising 2.5% of all malignant lymphomas (Freeman *et al.* 1972; Compagno and Oertel, 1980: Tupchong *et al.* 1986), and approximately 5% of thyroid malignant neoplasms (Staunton and Greening, 1973). In contrast to other types of non-Hodgkin's lymphomas(NHL), it is more common in elderly female cases (Burke *et al.* 1979; Grimley and Oates, 1980). The special features of this disease include the association with Hashimoto's thyroiditis, the frequency of isolated gastrointestinal relapse (Goudie and Angouridakis, 1970; Hamburger *et al.* 1983; Tsang *et al.* 1993) and controversy regarding the extent of surgical management.

The conventional approach to treatment of this disease has been to combine surgical resection and post-operative radiotherapy, which has induced a 30~70% overall survival rate(Staunton and Greening, 1976; Kapadia *et al.* 1982; Tennvall *et al.* 1987). However, with the development of multi-agent chemotherapy, combined chemo-radiotherapy has become more and more popular as initial therapy (Vigliotti *et al.* 1986; Skarsgard *et al.* 1991). This has brought into question the role of surgery as a primary treatment (Rosen *et al.* 1988).

Reviewing the clinical and laboratory features of our cases, we report our experiences, emphasizing early, and correct diagnosis and conservative evaluation of the optimal treatment for thyroid lymphoma.

MATERIALS AND METHODS

Five cases with primary thyroid lymphoma at the Yonsei University Medical Center (YUMC) were reviewed over a 13-year period between 1982 to 1994. Four cases were female and 1 was male, with a median age of 65 years (range: 52 to 72 years). The original bi-

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Departments of Internal Medicine[1], General Surgery[2], Radiation Oncology[3] and Pathology[4], Yonsei University College of Medicine, Seoul, Korea

Address reprint requests to Dr. JS Hahn, Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. box 8044, Seoul 120-752, Korea

opsy materials were re-evaluated and classified by NCI working formulation. Staging was done according to the Ann Arbor Criteria (Carbone *et al.* 1971). Staging work-up included history, physical examination, blood chemistry, chest X-ray, computed tomography, gallium scan, bone scan, bone marrow aspiration and biopsy.

A diagnostic lymph node biopsy or surgical intervention was performed in each of the five cases. Surgery entailed either a lobectomy or a subtotal-total thyroidectomy. Radiotherapy with 4,000~6,500 cGy tumor dosage was delivered using megavoltage equipment, encompassing the thyroid, cervical lymph nodes, supraclavicular fossa, and mediastinum with or without axillary fossa. Chemotherapy regimens consisted of cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincrinstine and prednisolone (CVP). Survival time was calculated from the time of initial treatment to the date of death or most recent follow-up date.

RESULTS

Patient characteristics

A non-tender growing neck mass with a less than seven month (median 2.8 month) history was the presenting symptom in all cases. One case presented as a growing mass with pressure symptoms, such as dyspnea, hoarseness and superior vena cava syndrome, and "B" symptom. Each of three cases presented as an enlarged thyroid gland in the form of a discrete nodule and the other two presented as a diffuse goiter. The median largest diameter of the tumor mass was 7.0 cm (range 5.5 ~ 11.0 cm), with the masses fixed to adjacent soft tissues in all five cases. The mass was confined to one lobe in three, while diffuse bilobar involvement was found in two. Lymphadenopathy was present in four cases, including four cervical lymphadenopathy, two supraclavicular lymphadenopathy, and one axillary lymphadenopathy. Mediastinal involvement was found in two cases (Table 1).

Three cases had a history of goiter and two of these had simultaneous Hashimoto's thyroiditis. In thyroid function test, three cases were in various stages of hypothyroidism. Anti-microsomal antibody was positive in 75% (3/4) and anti-thyroglobulin antibody was positive in 75%(3/4) of the cases. All five cases showed a sizable cold area in thyroid scan (Table 2). Fine needle aspiration biopsy (FNAB) was done in three cases; as an initial diagnostic procedure in two, and after regional

Table 1. Clinical fetures

	Number of cases(%)(n=5)
History of goiter	3(60)
Presenting symptoms	1(20)
dyspnea	1(20)
hoarseness	1(20)
SVC syndrome	1(20)
pain	1(20)
B symptoms	1(20)
Physical findings	
neck mass	5(100)
fixation	5(100)
mass>10 cm	2(40)
diffuse enlargement	2(40)
discrete nodule	3(60)
single lobe involvement	3(60)
right lobe	3(60)
bilobar involvement	2(40)
lymphadenopathy	4(80)
cervical adenopathy	4(80)
supraclavicular adenopathy	2(40)
axillary adenopathy	1(20)
mediastinal involvement	2(40)

SVC: superior vena cava

Table 2. Thyroid function

Hashimoto's thyroiditis	2/5(40%)
Thyroid function	
euthyroid	2/5(40%)
hypothyroid	3/5(60%)
Anti-microsomal antibody positivity	3/4(75%)
Anti-thyroglobulin antibody positivity	3/4(75%)
Thyroid scan	
Cold nodules	5/5(100%)

Table 3. Distribution by histology and stages

Stage	PDLL	DM	DL	Total
IE			1	1
IIE(non-mediastinal)		1	1*	2
IIE(mediastinal)	1		1*	2
Total	1	1	3	5

*clinical stage
PDLL: poorly differentiated lymphocytic lymphoma
DM: diffuse mixed
DL: diffuse large

Table 4. Treatment by stage

Stage	Surgery	Surger +Radio-therapy	Chemo −radio-therapy	Total
IE	1			1
IE (non-mediastinal)	1		1*	4
IIE (mediastinal)		1	1	
Total	2	1	2	5

*clinical stage

lymph node biopsy in one. The two initial FNAB results misdiagnosed as chronic inflammation in one patient and as papillary type carcinoma in another case; these were finally confirmed as lymphoma after surgery. Three cases underwent diagnostic/therapeutic partial or total thyroid resection on the impression of thyroid cancer. In the remaining two cases, the final diagnosis was established by open biopsy of enlarged cervical or supraclavicular lymph nodes. All five cases showed intermediate-grade non-Hodgkin's lymphoma (one poorly differentiated lymphocytic type, three diffuse large cell types, one diffuse mixed cell type) (Table3).

Treatment outcome

There was one case with stage I and four cases with stage II disease. Three cases had thyroidectomy including two cases with bilateral total thyroidectomy. Of three cases after surgery, one case received post-operative radiotherapy and two cases(one had a plan of radiotherapy) had no further treatment. Two cases were initially managed with combined chemo-radiotherapy resulting in one complete response and one partial response (Table 4). During chemo-radiotherapy, transient WHO grade II leukopenia and anemia occurred. Mild esophagitis was occurred in one case during radiotherapy. No fatal complications were encountered from four surgery and two chemo-radiotherapy. Among five cases, two were lost to follow-up at two and 31 months, respectively, and one died at 31 months (Table 5).

DISCUSSION

The usual clinical presentation of thyroid lymphoma is a rapidly growing thyroid mass, often with compressive symptoms of dysphagia, dyspnea, stridor or hoarseness. In concordance with other results (Compagno and Oertel, 1980; Ban *et al.* 1984; Tupchong *et al.* 1986), all five cases complained of a growing neck mass. The most common presentation form of thyroid mass was a discrete nodular shape. Approximately two-thirds of the cases in the available literature present with nodular shape while one-third show diffuse goiter (Hamburger *et al.* 1983; Aozasa *et al.* 1986). In our study, three cases had nodular and two were of diffuse types. Skarsgard *et al.* (1991) report 73% incidence of cervical or mediastinal lymphadenopathy. Similarly, two-thirds of our cases presented initially with lymphadenopathy. Two supraclavicular lymphadenopathy and one axillary lymphadenopathy were also found by Blair *et al.* (1985).

In 80~83% of thyroid lymphoma, Hashimoto's thyroiditis is associated (Hamburger *et al.* 1983; Aozasa *et al.* 1986) and symptoms of hypothyroidism are rare unless there is Hashimoto's thyroiditis. Two reports have documented an increased risk (up to 67 times) of thyroid lymphoma developing in cases with bi-

Table 5. Clinical findings, treatment and survival

Case	Age /Sex	Mass		Histology	Stage	Surgery	Radiotherapy	CT	Overall survival (months)
		Size (cm)	Duration (month)						
1	67/F	11	2.5	NHL PDLL	IIEA	lobectomy	mantle field 4000 cGy	–	lost in disease-free state at 30 months
2	65/F	7	2	NHL DL	IEA	total thyroidectomy		–	lost in disease-free state at 2 months
3	72/F	11	1	NHL DL	IIEB	–	entire neck & upper mediastinum 4500 cGy + tumor area 2000 cGy	CVP 1 cycle	alive in PR state for 11 months
4	52/F	5	7	NHL DL	IIEA	–	mantle field 1950 cGy entire neck & upper mediastinum 2520 cGy	CHOP 6 cycles	alive in disease-free state for 15 months
5	65/M	6	3	NHL DL	IIEA	total thyroidectomy		–	expired at 31 months

NHL: non-Hodgkin's lymphoma, PDLL: poorly differentiated lymphocytic lymphoma, DL: diffuse large, DM: diffuse mixed, PR: partial remission
CVP: cyclophosphamide+vincrinstine+prednisolone, CHOP: cyclophosphamide+adriamycin+vincrinstine+prednisolone, –: not done,

opsy-proved Hashimoto's thyroiditis (Holm *et al.* 1985; Kato *et al.* 1985). These frequent findings of co-existance were confirmed in our series; 40% of our patients had biopsy-proved Hashimoto's thyroiditis and 60% were in a hypothyroid state. Therefore, if an elderly case presents with a history of Hashimoto's thyroiditis that also has a rapidly growing thyroid nodule, thyroid lymphoma should be suspected. Hamburger *et al.* (1983) also suggested the following conditions as highly probable co-existing lymphoma in Hashimoto's thyroiditis cases without nodules: cold zone thyroid scan, rapidly growing goiter, enlargement of goiter even with thyroid hormone supplement, and painful, tender goiter with hoarseness.

Even when the diagnostic accuracy of a fine-needle aspiration biopsy(FNAB) increased to around 50~60% (Esselstyn and Crile, 1984; Skarsgard *et al.* 1991), chronic lymphocytic thyroiditis and small cell undifferentiated carcinoma(anaplastic carcinoma) have been confused with thyroid lymphoma (Mambo and Irwin, 1984). In our experience of two cases, the diagnoses were incorrect with FNAB. Taking into account our experience with FNAB, we prefer thyroid biopsy in cases where the clinical impression is of thyroid lymphoma. The rationale of the biopsy is that an incisional thyroid biopsy confirms the histological diagnosis with about a 90% accuracy rate. Moreover, it supplies a sufficient tissue supply for classification(Skarsgard *et al.* 1991).

Most of the thyroid lymphomas are of intermediate grade, especially the diffuse large cell type with a frequency rate of 60~90% by working formulation (Souhami *et al.* 1980; Aozasa *et al.* 1986), and 80~90% of this type of lymphoma is in stage I-II (Aozasa *et al.* 1986; Tsang *et al.* 1993). Maurer *et al.* (1979) comment that large non-cleaved cell type predominently shows localized disease, while immunoblastic type and small cleaved cell type usually show advanced disease. Similar results were obtained in our cases and all of our cases were intermediate grade with stage I-II disease.

The major role of surgery is the resection of operable disease so that minimal disease is present before radiotherapy. As tumors with gross residuals (more than 2.5 cm) have failed to achieve permanent local control in 35%, and an additional 23% showed distant recurrence as a first manifestation of relapse(Rosen *et al.* 1988), questions have been raised against the justification for extensive surgical intervention other than diagnostic biopsy in bulky stage I-II disease. Even if radiotherapy is combined with surgery, the five-year survival rate is still around 50~70% (Kapadia *et al.* 1982; Tennvall *et al.* 1987). In our experience of two cases with surgery alone, one died at 31 months, and one was lost to follow-up at two months. One case which received adjuvant radiotherapy with mantle field as Blair *et al.* (1985) suggested, was disease-free state at 30 month follow-up.

Chemotherapy has been traditionally utilized in stage III and IV disease and in salvage treatment. But a high recurrence rate after local treatment, preponderance of diffuse large cell type, and usage of doxorubicin-based regimens with high complete remission rate (65~80%) have led to the proposal of the use of multi-drug chemotherapy as an initial treatment even in stage I and II with adverse prognostic factors (Tupchong *et al.* 1986; Leedman *et al.* 1990; Skarsgard *et al.* 1991). Leedman *et al.* (1990) induced complete remission with initial chemotherapy even when the tumor was large and extra-thyroidal invasion was present. Tsang *et al.* (1993) induced 70% survival rate with combined chemo-radiotherapy in most of stage I-II cases and did radiotherapy alone only for a small group of stage I cases with a small tumor bulk. Rosen *et al.* (1988) suggested bulky and/or inoperable tumors may be more effectively managed with a combined regimen including chemo-radiotherapy. In our experience, one bulky inoperable stage IIE case received six cycles of CHOP chemotherapy which induced a complete tumor response. Another huge inoperable stage IIE case received one cycle of CVP regimen and radiotherapy which induced partial response. Our experience suggested the possible role of combined chemo-radiotherapy in bulky stage I-II thyroid lymphoma. Both patients with a chemotherapy regimen were tolerable with minor complications such as transient anemia and neutropenia.

Several studies demonstrate tumor bulk (> 10 cm) as the single most important prognostic factor in localized thyroid lymphoma (Rosen *et al.* 1988; Skarsgard *et al.* 1991; Tsang *et al.* 1993) due to local invasion and non-resectability. In our study, two cases showed huge masses(> 10 cm). Several unfavorable prognostic factors also have been recognized; advanced age (generally>60), signs of extra-thyroidal extension (hoarseness, stridor, dysphagia, dyspnea), tumor stage, mediastinal involvement, short duration (<six months) of thyroid mass, tumor fixation and histology(Aozasa *et al.* 1986; Tupchong *et al.* 1986). From earlier reports with the broad heading of histiocytic lymphoma, the histologic type did not predict longterm survival in thyroid lymphoma. However, with international working formulation, high-, intermediate- and low-grade thyroid lymphoma showed 13%, 79%, 92% five-year survival rate, respectively (Aozasa *et al.* 1986). Factors that have been associated with improved survival include intra-thyroidal disease (stage I), complete tumor resection, and associated Hashimoto's thyroiditis (Tupchong *et al.* 1986; Vigliotti *et al.* 1986). One stage IIE case with hoarseness, B symptoms, large size (11 cm), mediastinal involvement, extra-thyroidal lymphomatous involvement, and no associated-Hashimoto's thyroiditis showed only partial response after chemo-radiotherapy, while the other stage IIEA case with associated Hashimoto's thyroiditis had a complete response and was disease-free state for 15 months.

As the natural course of the thyroid lymphoma is the same as the other extra-nodal non-Hodgkin's lymphoma, our experience suggested that combined chemo-radiotherapy can be used as an initial treatment even when the patient presents with stage I, II with unfavorable prognostic factors. For the final therapeutic strategy in primary thyroid lymphoma, more case accumulating data is needed.

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