

ORIGINAL ARTICLE

Primary thyroid mucosa-associated lymphoid tissue lymphoma; a clinicopathological study of seven cases

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Purpose: Primary thyroid mucosa-associated lymphoid tissue (MALT) lymphoma is a very rare subgroup of thyroid lymphoma, accounting for about 6 to 28% of all primary thyroid lymphomas. The purpose of this study was to evaluate its clinicopathological features and treatment outcomes. **Methods:** We identified seven patients with thyroid MALT lymphoma who were treated between January 1997 and December 2007, and reviewed their clinicopathological features and follow-up outcomes. **Results:** There were five female and two male patients, and their mean age was 73 years. All patients presented with palpable neck mass. Two patients had hoarseness and dyspnea. All patients had a history of Hashimoto's thyroiditis with a mean of 175 months. Malignant lymphoma was suspected in only three patients using core needle biopsy. Four patients underwent thyroidectomy in the absence of preoperative pathologic confirmation, and histologic diagnosis was obtained after surgery. As initial treatment, complete surgical resection was performed in five patients, radiotherapy in one, and a combination of chemotherapy and radiotherapy in one. Six patients were alive for the mean follow-up period of 66 months and one patient died of unrelated causes. There were neither recurrences nor disease-specific mortalities. **Conclusion:** When primary thyroid MALT lymphoma occurs in the thyroid or is confined to the neck, it responds well to local treatment such as surgical resection and external beam radiation therapy.

Key Words: Primary thyroid MALT lymphoma, Hashimoto's thyroiditis, Diffuse large B-cell lymphoma

INTRODUCTION

Primary thyroid lymphoma is a rare condition accounting for 1 to 5% of all thyroid malignancies and approximately 2% of all malignant extranodal lymphomas [1]. Mucosa-associated lymphoid tissue (MALT) lymphoma is one of the rare variants, first described by Isaacson and

Wright in 1984 [2]. Pure thyroid MALT lymphomas comprise about 6 to 28% of primary thyroid lymphomas, and are recognized as extranodal marginal zone B-cell lymphomas in the Revised European American Lymphoma classification of 1994 and the World Health Organization classification of 1999 [3-5]. Strictly, the thyroid gland is not a mucosal organ, being of foregut origin, and the lym-

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phoid tissue that accumulates in the thyroid in Hashimoto's thyroiditis shares features with MALT. MALT lymphomas are thought to develop from lymphocytic tissue acquired during the course of a chronic inflammatory or autoimmune process. The thyroid is normally devoid of such lymphocytic tissue, and chronic autoimmune thyroiditis (Hashimoto's disease) has been associated with an increased risk of lymphoma, including MALT lymphoma [6]. The coexistence of reactive and neoplastic processes in the thyroid gland may render the cytological and histological diagnosis of MALT lymphoma difficult. Clinically, most patients present in the seventh decade of life and 30 to 50% of patients have compression symptoms, including dysphagia, dyspnea, stridor or hoarseness [7]. Primary thyroid MALT lymphomas are known to respond better to local treatments such as surgical resection and radiotherapy, compared to diffuse large B-cell lymphomas. Also, primary thyroid MALT lymphomas tend to run an indolent clinical course with excellent prognosis, whereas exclusive diffuse large B-cell types or mixed types display a more aggressive clinical course [8]. The present study aimed to evaluate the clinicopathological features and treatment outcomes of patients with primary thyroid MALT lymphoma.

METHODS

We identified seven patients with a pathologic diagnosis of thyroid MALT lymphoma between January 1997

and December 2007, and reviewed their clinicopathological characteristics and treatment outcomes retrospectively. The diagnosis of MALT lymphoma was given in cases with the presence of CD20 immunoreactivity in immunohistochemically stained specimens from fine needle aspiration biopsy (FNAB), core biopsy and surgery, and the histologic presence of small lymphoid cells with variable proportions of centrocyte-like cells, plasma cells, lymphoplasmacytoid lymphocytes, monocytoid B-cells, and interspersed large transformed lymphocytes. Mixed types with simultaneous presence of both MALT lymphoma and diffuse large B-cell lymphoma were excluded. We also investigated the patients' stage (according to the Ann Arbor staging system) by examining the results from physical examination, blood counts, chemistry, chest X-rays, chest computed tomography (CT) scan, abdominal-pelvic CT, and bone marrow examination. This study was approved by our institutional review board. We adopted Musshoff's modification of the Ann Arbor staging system, and primary thyroid lymphomas were staged as follows: IE: primary thyroid lymphoma with or without extension into the perithyroidal soft tissue; IIE: primary thyroid lymphomas with involvement of lymph nodes on the same side of the diaphragm; IIIE: primary thyroid lymphomas with involvement of lymph nodes on both sides of the diaphragm and/or spleen; and IVE: primary thyroid lymphomas with dissemination to other extranodal sites [9]. Although this study was not primarily focused on staging, some authors insist that primary thyroid lymphoma is defined as a lymphoma that only involves the thy-

Table 1. Clinical characteristics of primary thyroid mucosa-associated lymphoid tissue lymphoma cases

Patient	Sex	Age	Diagnostic tool	Stage	Treatment modality	Duration of Hashimoto's	Follow-up
1	F	85	Core biopsy	IE	RTx	240 mo	Alive 37 mo
2	M	57	Core biopsy	IE	CTx, RTx	60 mo	Alive 62 mo
3	M	62	FNAB, surgery	IIE	Surgery (TT with MRND)	120 mo	Alive 143 mo
4	F	72	Surgery	IIE	Surgery (TT with MRND)	360 mo	Expired (pancreatic cancer) 25 mo
5	F	77	Core biopsy	IE	Surgery (HT)	144 mo	Alive 38 mo
6	F	75	Surgery	IE	Surgery (TT)	120 mo	Alive 10 mo
7	F	64	Surgery	IE	Surgery (TT)	180 mo	Alive 148 mo

FNAB, fine needle aspiration biopsy; RTx, radiotherapy; CTx, chemotherapy; TT, total thyroidectomy; MRND, modified radical neck dissection; HT, hemithyroidectomy.

roid gland or the thyroid gland with its adjacent lymph nodes [10], restricting its stage to either stage IE or IIE under the Ann Arbor staging system. The mean follow-up period was 66 months (range, 10 to 148 months).

RESULTS

The patients' characteristics are listed in Table 1. There were five female and two male patients. At the time of diagnosis, the mean age of the patients was 73 years (range, 57 to 85 years). All patients complained of palpable neck masses, and two patients also had hoarseness and dyspnea. All patients had a history of autoimmune Hashimoto's thyroiditis, with a mean duration of 175 months (range, 60 to 360 months). One patient underwent FNAB, though the results were reported to be non-diagnostic. Core biopsy was performed in three cases for pathologic

confirmation. Four cases, including the FNAB case, directly proceeded with curative surgery in the absence of preoperative pathologic confirmation because they displayed signs of acute enlargement as well as dysphagia and dyspnea during outpatient department follow-up, along with character changes in ultrasonography. Diagnosis was confirmed after surgery. The preoperative goitrous condition, postoperative gross specimen and microscopic feature (patient No.6) are shown in Fig. 1. As initial treatment, complete surgical resection was performed in five cases, radiotherapy alone in one case, and a combination of chemotherapy and radiotherapy was given in one case. Among the patients that underwent surgery, there were two cases of total thyroidectomy, two cases of total thyroidectomy with modified radical neck dissection, and one case of hemithyroidectomy. The radiotherapy-only case was performed using a dose of 4,500 cGy to the neck area. In the case of the patient that underwent combined chemo-

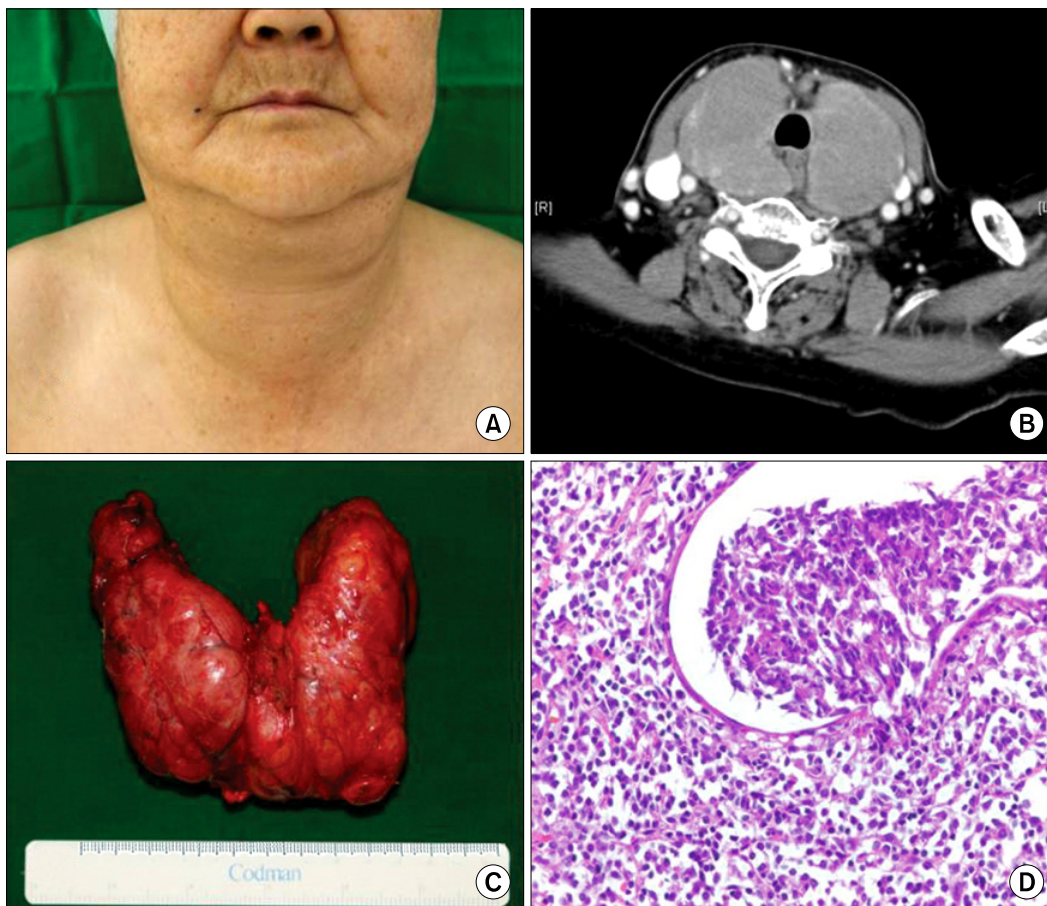


Fig. 1. (A) Gross appearance of patient, (B) computed tomography scan showing homogeneously enlarged thyroid gland. (C) Specimen showing firm, enlarged thyroid gland, and (D) microscopic features of mucosa-associated lymphoid tissue lymphoma (H&E, × 100).

therapy and radiotherapy, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen was performed and the radiation dose was 4,500 cGy at the lesion. Using the Ann Arbor staging system, five patients were stage IE and two patients were stage IIE. All of the patients achieved complete remission. One patient expired due to an unrelated cause (pancreatic cancer), and there were no disease-specific mortalities.

DISCUSSION

MALT lymphomas are very rare, but account for 85% of extranodal non-Hodgkin's lymphomas [2]. Although the stomach is by far the most common site of MALT lymphomas, they have also been described in various non-gastrointestinal sites, such as the salivary gland, thyroid, skin, conjunctiva, orbit, lung, breast, kidney, liver and even in the intracranial dura [11-18].

Two types of MALT can be identified in disparate organs that do not correspond to peripheral sites of the immune system. The native type consists of lymphoid tissue physiologically present in the gut (e.g., Peyer's patches), whereas acquired MALT develops in sites of inflammation in response to either infectious conditions such as *Helicobacter pylori* gastritis, or autoimmune processes such as Hashimoto's thyroiditis [19,20]. In addition to being a causal factor of primary thyroid MALT lymphoma, it has been hypothesized that Hashimoto's thyroiditis may further develop into aggressive lymphomas [6,21]. This is the basis for treatment of primary thyroid MALT lymphomas, even though they have a better response to local treatment and a more favorable prognosis compared to diffuse large cell lymphomas.

Normally, FNAB is a widely accepted technique for the diagnosis of thyroid nodules. However, primary thyroid lymphomas can be difficult to diagnose with FNAB alone. While the diagnostic accuracy of FNAB is quite low for diffuse large B-cell lymphomas, it is even lower in the case of thyroid MALT lymphomas because the differentiation of MALT lymphomas from Hashimoto's thyroiditis can be difficult by cytomorphology alone [22]. Core needle biopsy, though not considered a first-line method for the diag-

nosis of lymphomas, has been reported to have a higher diagnostic yield, with a sensitivity of 94.3%, a specificity of 100%, and an accuracy of 95.2% [23]. As a method for diagnostic confirmation, core needle biopsy would be an alternative with a high priority along with FNAB. In our study, surgery was performed on a total of four cases prior to pathological confirmation, with a single case of FNAB and three cases of core needle biopsy. Clinically, when a patient with a past history of Hashimoto's thyroiditis displays signs of abrupt thyroid enlargement or compression symptoms, the possibility of thyroid MALT lymphoma should be considered. This is especially true for the patients with a history over 5 years.

The optimal treatment modality for primary thyroid MALT lymphoma remains yet to be defined. The benefits of surgical treatment in diffuse large B-cell lymphoma still remain in debate. While the combination of radiotherapy and chemotherapy is currently known as the standard treatment modality, local treatments such as total thyroidectomy, or sole radiotherapy have been reported to be effective as well in MALT lymphoma limited to the thyroid [3,24]. There are some authors who advocate that the treatment of neck lymph nodes with signs of metastasis from primary thyroid lymphoma should include adjuvant radiotherapy in addition to surgery such as functional neck dissection [8]. The five cases of MALT lymphoma in this study that were localized to the thyroid did not show recurrence or disease-related mortality regardless of treatment modality. Also, the two cases (stage IIE) that underwent modified radical neck dissection due to metastatic neck lymph nodes showed good outcome without additional adjuvant treatment. All of the patients remained recurrence free after 10 years. Considering the excellent prognosis achieved in the two cases with lateral neck node metastasis by complete surgical resection without adjuvant treatment, it can be said that complete surgical removal has significant value in treating primary thyroid MALT lymphomas even with regional lymph node metastasis. There are other similar reports where MALT lymphoma showed an indolent nature with an overall survival rate of more than 90% after only local control, whereas cases of diffuse large B-cell lymphoma had an overall survival rate of 30 to 50% even with both surgery and

diotherapy performed [7,25,26]. Considering the results of the current study and previous reports, the most important modality for the treatment of localized primary thyroid MALT lymphoma will be complete loco-regional control of disease including surgical removal and radiation therapy. Currently, there are no set protocols concerning follow-up evaluations after the treatment of primary thyroid MALT lymphoma. There are cases where fluorine-18 fluorodeoxyglucose-positron emission tomography scans were used in the evaluation of recurrences, but its utility is yet to be determined [27].

In conclusion, when primary thyroid MALT lymphoma is suspected, core needle biopsy along with FNAB should be considered as a first-line histologic diagnostic tool. As initial treatment, local treatment, such as complete surgical resection and radiotherapy, should be performed when the disease is localized in the thyroid or when the metastasis is limited to the regional lymph nodes. The role of adjuvant radiotherapy and chemotherapy is still undetermined and is in need of further research.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

- Pedersen RK, Pedersen NT. Primary non-Hodgkin's lymphoma of the thyroid gland: a population based study. *Histopathology* 1996;28:25-32.
- Isaacson P, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. *Cancer* 1984;53:2515-24.
- Thieblemont C, Mayer A, Dumontet C, Barbier Y, Callet-Bauchu E, Felman P, et al. Primary thyroid lymphoma is a heterogeneous disease. *J Clin Endocrinol Metab* 2002;87:105-11.
- Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361-92.
- Jaffe ES, Harris NL, Diebold J, Muller-Hermelink HK. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. A progress report. *Am J Clin Pathol* 1999;111(1 Suppl 1):S8-12.
- Hyjek E, Isaacson PG. Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. *Hum Pathol* 1988;19:1315-26.
- Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS, Abbondanzo SL. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *Am J Surg Pathol* 2000;24:623-39.
- Widder S, Pasiaka JL. Primary thyroid lymphomas. *Curr Treat Options Oncol* 2004;5:307-13.
- Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31:1860-1.
- Ansell SM, Grant CS, Habermann TM. Primary thyroid lymphoma. *Semin Oncol* 1999;26:316-23.
- Zinzani PL, Magagnoli M, Galieni P, Martelli M, Poletti V, Zaja F, et al. Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. *J Clin Oncol* 1999;17:1254.
- Kaplan MA, Pettit CL, Zukerberg LR, Harris NL. Primary lymphoma of the trachea with morphologic and immunophenotypic characteristics of low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *Am J Surg Pathol* 1992;16:71-5.
- Nicholson AG, Wotherspoon AC, Diss TC, Butcher DN, Sheppard MN, Isaacson PG, et al. Pulmonary B-cell non-Hodgkin's lymphomas. The value of immunohistochemistry and gene analysis in diagnosis. *Histopathology* 1995;26:395-403.
- Isaacson PG, Chan JK, Tang C, Addis BJ. Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue arising in the thymus. A thymic lymphoma mimicking myoepithelial sialadenitis. *Am J Surg Pathol* 1990;14:342-51.
- Mattia AR, Ferry JA, Harris NL. Breast lymphoma. A B-cell spectrum including the low grade B-cell lymphoma of mucosa associated lymphoid tissue. *Am J Surg Pathol* 1993;17:574-87.
- Wotherspoon AC, Hardman-Lea S, Isaacson PG. Mucosa-associated lymphoid tissue (MALT) in the human conjunctiva. *J Pathol* 1994;174:33-7.
- Parveen T, Navarro-Roman L, Medeiros LJ, Raffeld M, Jaffe ES. Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue arising in the kidney. *Arch Pathol Lab Med* 1993;117:780-3.
- Kumar S, Kumar D, Kaldjian EP, Bauserman S, Raffeld M, Jaffe ES. Primary low-grade B-cell lymphoma of the dura: a mucosa associated lymphoid tissue-type lymphoma. *Am J Surg Pathol* 1997;21:81-7.
- Zucca E, Bertoni F, Roggero E, Cavalli F. The gastric marginal zone B-cell lymphoma of MALT type. *Blood* 2000;96:410-9.
- Isaacson PG. Gastric MALT lymphoma: from concept to cure. *Ann Oncol* 1999;10:637-45.
- Isaacson PG. Mucosa-associated lymphoid tissue lymphoma. *Semin Hematol* 1999;36:139-47.
- Sangalli G, Serio G, Zampatti C, Lomuscio G, Colombo L. Fine needle aspiration cytology of primary lymphoma of

- the thyroid: a report of 17 cases. *Cytopathology* 2001;12: 257-63.
23. Screation NJ, Berman LH, Grant JW. Head and neck lymphadenopathy: evaluation with US-guided cutting-needle biopsy. *Radiology* 2002;224:75-81.
 24. Tsang RW, Gospodarowicz MK, Pintilie M, Wells W, Hodgson DC, Sun A, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003;21:4157-64.
 25. Laing RW, Hoskin P, Hudson BV, Hudson GV, Harmer C, Bennett MH, et al. The significance of MALT histology in thyroid lymphoma: a review of patients from the BNLI and Royal Marsden Hospital. *Clin Oncol (R Coll Radiol)* 1994;6: 300-4.
 26. Vigliotti A, Kong JS, Fuller LM, Velasquez WS. Thyroid lymphomas stages IE and IIE: comparative results for radiotherapy only, combination chemotherapy only, and multimodality treatment. *Int J Radiat Oncol Biol Phys* 1986;12:1807-12.
 27. Mikosch P, Würtz FG, Gallowitsch HJ, Kresnik E, Lind P. F-18-FDG-PET in a patient with Hashimoto's thyroiditis and MALT lymphoma recurrence of the thyroid. *Wien Med Wochenschr* 2003;153:89-92.