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Clinicopathologic Characteristics and *A20* Mutation in Primary Thyroid Lymphoma

Yasuko Kuribayashi-Hamada[1], Mariko Ishibashi[2], Atsushi Tatsuguchi[3], Toshio Asayama[1], Namiko Takada-Okuyama[1], Asaka Onodera-Kondo[1], Keiichi Moriya[1], Takehito Igarashi[4], Hiroyuki Onose[5], Sakae Tanosaki[6], Norio Yokose[7], Hiroki Yamaguchi[1] and Hideto Tamura[1,8]

[1]Department of Hematology, Nippon Medical School, Tokyo, Japan
[2]Department of Microbiology and Immunology, Nippon Medical School, Tokyo, Japan
[3]Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan
[4]Department of Endocrine Surgery, Nippon Medical School, Tokyo, Japan
[5]Division of Endocrinology, Kanaji Hospital, Tokyo, Japan
[6]Division of Hematology, The Fraternity Memorial Hospital, Tokyo, Japan
[7]Division of Hematology, Department of Medicine, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan.
[8]Division of Diabetes, Endocrinology and Hematology, Department of Internal Medicine, Dokkyo Medical University Saitama Medical Center, Saitama, Japan

Background: Primary thyroid lymphoma (PTL) is a rare disease frequently arising against a background of autoimmune thyroiditis. It has recently been reported that the inactivation of the NF-κB negative regulator *A20* by deletion and/or mutation could be involved in the pathogenesis of subsets of B-cell lymphomas. This study investigated the clinicopathologic characteristics and *A20* mutation in patients with PTL.

Methods: We analyzed the characteristics of 45 PTL patients (14 men and 31 women), with a median age of 71 (range, 35-90) years. *A20* mutations were analyzed in DNA extracted from 20 samples consisting of 19 tumor tissue samples and 1 sample from Hashimoto's thyroiditis.

Results: Thirty-five patients (82%) had a history of Hashimoto's thyroiditis, and 29 (64%) had diffuse large B-cell lymphoma (DLBCL) and presented with larger tumors including bulky mass, elevated soluble interleukin-2 receptor levels, and a longer history of Hashimoto's thyroiditis than that of patients with mucosa-associated lymphoid tissue (MALT) lymphoma (n=16). *A20* mutations were identified in 3 of 19 PTL patients (16%), in 2 of the 10 (20%) with DLBCL and in 1 of the 9 (11%) with MALT lymphoma. Interestingly, all patients with *A20* mutations had Hashimoto's thyroiditis. Furthermore, they had a common missense variant in exon 3 (rs2230926 380T>G; F127C), which reduces the ability of *A20* to inhibit NF-κB signaling.

Conclusion: Our study suggests that the histological features of PTL affect clinical outcomes and that *A20* mutations are related to PTL pathogenesis in some patients with Hashimoto's thyroiditis.

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Key words: primary thyroid lymphoma, *A20* mutation, mucosa-associated lymphoid tissue (MALT) lymphoma, Hashimoto's thyroiditis

Introduction

Primary thyroid lymphoma (PTL) represents approximately 5% of all thyroid malignancies, 1-2.5% of all malignant lymphomas, and less than 2% of extranodal lymphomas[1,2]. Several reports showed that PTL patients were predominantly female, often in their 60s, and had

Correspondence to Hideto Tamura, MD, PhD, Department of Hematology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: tam@nms.ac.jp
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limited-stage disease and a good prognosis[3–7]. PTL is a heterogeneous disease, however. PTL patients have not been fully characterized, and no standard treatment has been established because there has been no randomized trial of treatment. PTL frequently develops in persons with autoimmune thyroid disease, especially Hashimoto's thyroiditis, which is a reported risk factor for PTL[8,9]. Thus, pathogenesis is likely related to longstanding chronic inflammation and autoimmune disturbance[2], although the details remain to be clarified.

The NF-κB negative regulator *A20*, also called tumor necrosis factor-α-induced protein 3 (TNFAIP3), encodes a ubiquitin-editing enzyme that restricts NF-κB-dependent signaling and plays a key role in negative regulation of inflammation and immunity[10,11]. Polymorphisms of the *A20* gene locus have been identified as risk factors in multiple human autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus[12,13]. *A20* inactivation by deletion and/or mutation has recently been reported to be involved in the pathogenesis of subsets of B-cell lymphomas, especially mucosa-associated lymphoid tissue (MALT) lymphoma[14,15]. Honma et al. reported that *A20* deletion occurred frequently in diffuse large B cell lymphoma (DLBCL) (38%) and ocular adnexa MALT (37.5%) but rare in stomach MALT (6.9%) and unreported in PTL[16]. Another study reported *A20* deletion in MALT lymphoma of the ocular adenoxa (8 of 42 cases, 19%), salivary gland (2 of 24 cases, 8%), and thyroid gland (1 of 9 cases, 11%)[17]. Very few studies have investigated *A20* mutations in PTL[18,19]. On the basis of previous findings, we hypothesized that *A20* abnormalities may be related to PTL pathogenesis, which is very often associated with chronic thyroiditis. In this study, we analyzed the clinicopathologic characteristics of PTL and the characteristics of *A20* gene polymorphisms in PTL patients.

Materials and Methods

Patients and Thyroid Specimens

We analyzed the clinicopathologic characteristics of 45 PTL patients who were diagnosed and classified according to the 2008 World Health Organization classification in our 4 institutions during the period from 2002 to 2016. This study was approved by the Institutional Review Boards of all the participating institutions. PTL is defined as a lymphoma mainly involving the thyroid gland, without/with involvement of the lymph nodes, including regional neck lymph nodes. In one institution (Nippon Medical School, approval number 27-03-563), DNA samples were extracted from fresh thyroid tissues, and smears were prepared from bone marrow mononuclear cells (BMMCs) without lymphoma involvement, after obtaining written informed consent for participation from each patient. Thyroid tissues obtained by thyroidectomy were homogenized with a glass homogenizer in RPMI 1640 medium (Wako Pure Chemical Industries, Osaka, Japan) and then stored at −80°C until use. The control DNA was extracted from peripheral blood mononuclear cells of consenting participants who were originally suspected of having the disease but later confirmed to be PTL negative.

DNA Extraction, PCR, and Sequencing Analysis

DNA was extracted from frozen tissues and smear preparations of BMMCs by using the QIAamp DNA Mini kit and Gentra Puregene Tissue kit (Qiagen, Hilden, Germany), respectively, according to the manufacturer's instructions. The coding exons 2-9 of the *A20* gene were amplified from DNA with PCR primers[14] using PrimeSTAR GXL DNA Polymerase (Takara Bio Inc., Shiga, Japan). PCR products were purified using the FastGene Gel/PCR Extraction Kit (Nippon Genetics Co. Ltd., Tokyo, Japan). Direct sequencing was performed using the Big Dye Termination 3.1 kit and ABI PRISM 310 Genetic Analyzer (Life Technologies, Carlsbad, CA, USA).

Immunohistochemical Staining

Formalin-fixed, paraffin-embedded thin sections (4 μm thick) were immersed in 0.3% H_2O_2/methanol for 30 min to block endogenous peroxidase activity and microwaved in Tris-EDTA buffer (pH 9.0) for antigen retrieval. After blocking with 10% normal goat serum for 10 min at 37°C, sections were incubated with 100-fold diluted rabbit polyclonal antibody for NF-κB p65 (phospho S536; ab 86299; Abcam, Cambridge, UK) at 4°C for 18 h and then stained with 100-fold diluted biotinylated anti-rabbit IgG (Santa Cruz Biotechnology, Dallas, TX, USA) for 30 min at 25°C, followed by avidin-biotin peroxidase complex (Santa Cruz Biotechnology) staining. The sections were reacted with a 3,3′-diaminobenzidine tetrahydrochloride (DAB) solution containing 0.03% H_2O_2 and counterstained with Mayer's hematoxylin.

Statistical Analysis

The χ^2 test was used for comparisons of 2 groups. A P value of less than 0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

The patients' characteristics are shown in **Table 1**. They

Table 1 Patient characteristics at the time of diagnosis of PTL

Variable	
Patients, n	45
Age, years (median [range])	71 [35–90]
Gender (male/female), n	14/31
Diagnosis by pathological view, n (%)	
DLBCL	29 (67)
MALT	16 (33)
Concomitant thyroid disease, n (%)	
Hashimoto's thyroiditis	35 (80)
Basedow's disease	2 (4)
None	7 (16)
Symptoms at diagnosis, n	
Growing nodular goiter	39
Hoarseness	4
B symptoms	2
No symptoms	3
Laboratory data at diagnosis, median (range)	
LDH (IU/mL)	198 (117–433)
sIL-2R (IU/mL)	478 (130–3,189)
TSH (U/mL)	3.91 (0.12–185.459)
Free T4 (pmol/L)	1.10 (0.14–1.74)
Clinical stage[a)], n (%)	
IE	28 (62)
IIE	13 (29)
III, IV	4 (9)
A20 abnormalities, n (% in tested cases)	3 (16)

DLBCL: diffuse large B-cell lymphoma; MALT: mucosa-associated lymphoid tissue; LDH: lactate dehydrogenase; sIL-2R: soluble interleukin-2 receptor; TSH: thyroid-stimulating hormone.
a) Clinical stage IE was defined as lymphoma limited to the thyroid gland, IIE as the thyroid gland and regional lymph nodes above the diaphragm, IIIE as the thyroid gland and regional lymph nodes above and below the diaphragm, and IV as disseminated nodal and/or additional extranodal involvement.

included 14 men and 31 women (median age, 71 years; range, 35-90 years) presenting with a growing nodular goiter (n=39), hoarseness (n=4), and B symptoms (n=2). Three patients who had no symptoms related to lymphoma or thyroiditis were diagnosed when a low-echoic tumor was detected in ultrasound scanning performed during a follow-up examination for Hashimoto's thyroiditis. The pathologic diagnosis of PTL included DLBCL (n=29) and MALT lymphoma (n=16). Thirty-five patients (80%) had Hashimoto's thyroiditis, and 11 of the 35 were diagnosed concurrently with lymphoma, as indicated by elevated thyroglobulin antibody and/or thyroid peroxidase antibody levels. Hashimoto's thyroiditis was more frequent among MALT lymphoma patients (93%) than among DLBCL patients (71%). Twenty-eight patients (62%) had stage IE disease and 13 (29%) had stage IIE disease; only 4 patients had advanced disease.

The results of comparative analysis of DLBCL and MALT patients are shown in **Table 2**. Compared with patients with MALT lymphoma, DLBCL patients presented with significantly larger tumors including bulky mass (> 10 cm). The median interval between the time of diagnosis of Hashimoto's thyroiditis and PTL was 84 months, when 11 patients concurrently diagnosed with Hashimoto's thyroiditis and PTL were excluded. Interestingly, DLBCL patients had a significantly longer history of Hashimoto's thyroiditis and higher levels of serum soluble IL-2 receptor than did MALT lymphoma patients.

Patients with MALT lymphoma were treated with thyroidectomy or hemithyroidectomy and postoperative radiotherapy. DLBCL patients were treated with chemotherapy after surgery, followed by radiotherapy or no additional treatment. The treatment protocol was 6 cycles of chemotherapy consisting of R-CHOP (rituximab, cyclo-

Table 2 Comparative analysis of PTL with DLBCL and MALT lymphoma

	DLBCL	MALT	P value
Patients, n	29	16	
Age (≥65/<65 years)	25/4	11/5	NS
Gender (male/female)	10/19	4/12	NS
Performance status (0–1/2–4)	23/3	12/0	NS
Hoarseness at diag. (yes/no)	3/25	1/13	NS
Symptomatic/asymptomatic	28/1	12/2	NS
Clinical stage (I, II/III, IV)	26/3	15/1	NS
Tumor size (≥5 cm/<5 cm)	20/6	6/8	0.031
Bulky mass (yes/no)	4/22	0/14	NS
Hashimoto's thyroiditis (yes/no)	20/8	14/1	0.092
Duration of Hashimoto's thyroiditis (>84 months/<84 months)	9/11	1/10	0.041
LDH (>UNL/ =<UNL)	14/14	4/10	NS
sIL-2R (>UNL/≤UNL)	22/6	5/8	0.011

DLBCL: diffuse large B-cell lymphoma; MALT: mucosa-associated lymphoid tissue; LDH: lactate dehydrogenase; sIL-2R: soluble interleukin-2 receptor; NS: not significant.

phosphamide, vincristine, prednisolone, and doxorubicin), THP-COP (pirarubicin instead of doxorubicin; for elderly patients), or 3 cycles of chemotherapy with locoregional radiation.

Survival and Outcome of PTL Patients

The overall treatment response rate was 96%, and 2 DLBCL patients did not respond to initial treatment. The median duration of follow-up was 42 months (range, 2-229 months). During follow-up only 3 DLBCL patients died, from lymphoma dissemination in the central nervous system or complications during chemotherapy, namely, acute myocardial infarction and pneumonia. Five patients relapsed during follow-up. Three DLBCL patients who relapsed in the residual thyroid lobe underwent thyroidectomy, and 2 of the 3 received postoperative radiotherapy and achieved a second complete remission. All patients with MALT lymphoma were alive at the median 63-month follow-up (range, 3-122 months), although 1 patient relapsed and was diagnosed with DLBCL transformed from MALT lymphoma 3 years after the initial thyroidectomy.

***A20* Mutation in PTL Patients**

We analyzed *A20* mutations in tumor cells (somatic cells) from 19 PTL patients and in nontumor cells (germline cells) from patients with Hashimoto's thyroiditis. Three of the 19 patients (16%) had a missense point mutation in exon 3 (380T>G transition), which leads to replacement of phenylalanine with cysteine at amino acid position 127 (F127C; SNP accession no. rs2230926; **Fig. 1a** and **Table 3**). Of those 3 patients, 2 had DLBCL and 1 had MALT lymphoma with Hashimoto's thyroiditis (**Table 4**). The heterozygous *A20* mutation of 1 patient's (no. 1 in **Table 3**) sample was identified not only in tumor cells but also in nontumor (germline) cells from the BMMC smears without involvement of DLBCL. PTL tissue from patient no. 3 had a homozygous mutation in *A20*, while nontumor BMMCs showed a heterozygous mutation (**Fig. 1b** and **Table 3**). We did not obtain a BMMC sample from patient no. 2 and thus were unable to identify the *A20* mutation in germline DNA from that patient. The *A20* F127C mutation was reported to lead to inactivation of *A20* and results in constitutive NF-κB activation[20]. Consistent with this previous report, immunohistochemical staining showed that the phosphorylated NF-κB p65 protein was strongly expressed in the PTL tissue from that patient (no. 1 in **Table 3**), in contrast to normal thyroid tissue (**Fig. 2**). Furthermore, even in this small sample, soluble IL-2 receptor levels tended to be higher in patients with the *A20* mutation than in those without the mutation (data not shown).

Discussion

We examined the characteristics and clinical course of 45 PTL patients and results regarding genetic or somatic abnormality of *A20*. PTL is more frequent in middle-aged and older women, which is the age group and gender of most patients with Hashimoto's thyroiditis. Eighty percent of the present patients had a past history of Hashimoto's thyroiditis, and 64% had the DLBCL histologic type. None had received a diagnosis of T-cell lymphoma, and most had limited-stage disease. The clinical characteristics of our patients were consistent with those described in previous reports[1], and the frequency of *A20* mutations in PTL was similar to that in other lympho-

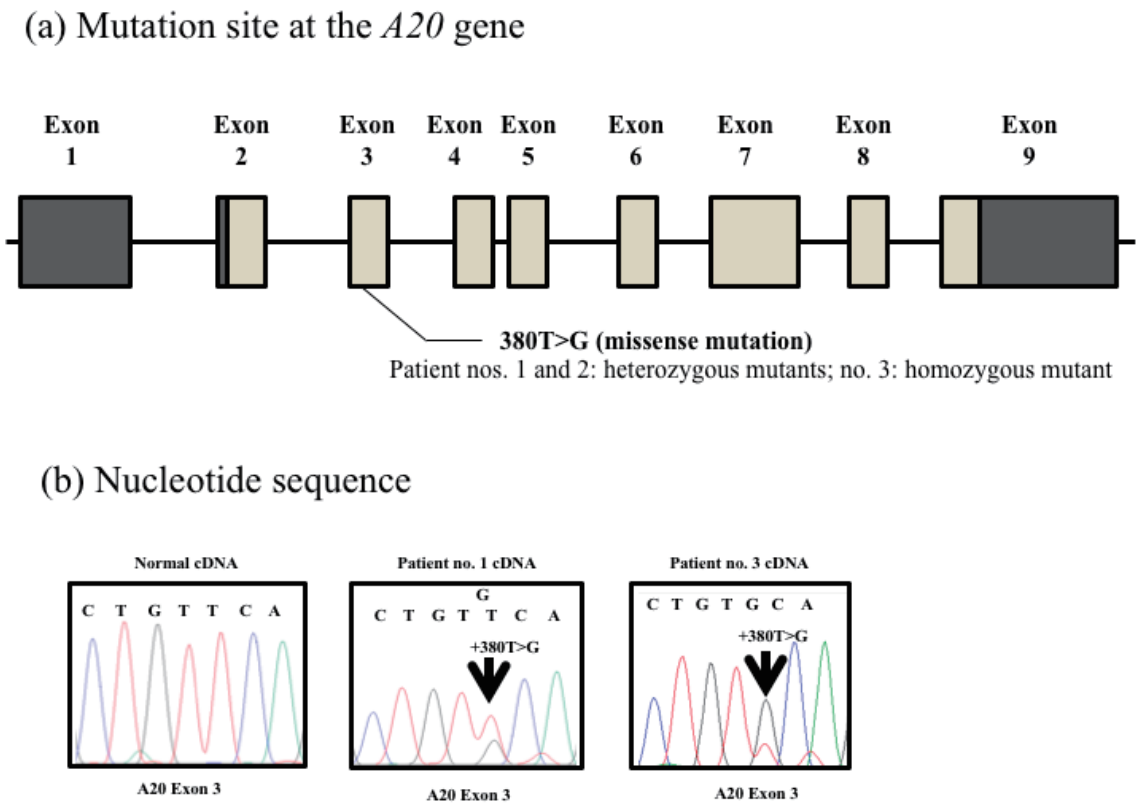

Fig. 1 *A20* mutation in PTL patients. (a) The mutation site at the human *A20* gene in this study. The *A20* gene (upper schematic diagram) comprises 9 exons, and the first exon is noncoding. The A20 protein (lower schematic diagram) has an OUT domain and a zinc finger (ZF) domain, which have deubiquitinating and E3 ligase activity, respectively. The location of gene and amino acid conversions is represented on the map by triangles. (b) Electrofluorograms of the *A20* exon3 genomic DNA (gDNA) sequence of the PTL patient samples and normal control samples. gDNA of BMMCs was used as germline DNA in PTL patients. Arrows indicate sites of nucleotide change (380T>G). (c) The mutation sites at the human *A20* protein in this study.

Table 3 Patients with the *A20* F127C mutation

Pt no.	Gender	Age	Diag	St	HT* (months)	Lymphoma tissue	BMMC
						Mutation type	
1	F	68	DLBCL	IA	4	Heterozygous	Heterozygous
2	M	67	MALT	IA	48	Heterozygous	No data
3	F	71	DLBCL	IIA	82	Homozygous	Heterozygous

HT*, time since the diagnosis of Hashimoto's thyroiditis at the time of diagnosis of PTL.
Pt, patient; Diag, diagnosis; St, stage; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; BMMC, bone marrow mononuclear cell.

Table 4 Patients with/without the *A20* mutation

A20 mutation	+	–
Patients, n	3	16
Diagnosis, MALT/DLBCL	1/2	8/8
Median age, years (range)	68 (67–71)	74 (35–83)
Gender, male/female	1/2	8/8
Clinical stage, I+II/III+IV	3/0	13/3
Median maximal tumor mass diameter, mm (range)	46 (27–93)	69 (20–100)
Hashimoto's thyroiditis, yes/no	3/0	15/3
Median duration of Hashimoto's thyroiditis, years (range)	4 (1–8)	8 (1–30)
LDH, median (range) (U/mL)	179 (122–336)	232 (176–422)
sIL-2R, median (range) (U/mL)	1,219 (1,148–1,289)	653 (130–3,189)

DLBCL: diffuse large B-cell lymphoma; MALT: mucosa-associated lymphoid tissue; LDH: lactate dehydrogenase; sIL-2R: soluble interleukin-2 receptor.

mas[16,17].

Because there has been no randomized trial of therapies for PTL, we usually treat affected patients by using the guidelines for non-Hodgkin lymphomas. In our study, patients with MALT lymphoma responded well to surgery and local radiation. Most DLBCL patients were treated with combined chemotherapy, following the strategy for nodular lymphoma, but some had a more aggressive clinical course, as previously reported[21]. Three DLBCL patients relapsed in the residual thyroid lobe and were successfully treated with surgery and/or radiation. Although further research is needed to determine the optimal treatment and prognostic factors for PTL, our results suggest that local control is important for aggressive and indolent lymphoma.

Compared with MALT lymphoma patients, DLBCL patients had a longer history of Hashimoto's thyroiditis before diagnosis of lymphoma. Similarly, some observational studies of chronic thyroiditis reported an interval between diagnosis of Hashimoto's thyroiditis and lymphoma onset of 4-9 years, and the interval to aggressive lymphoma was reported to be longer still[8,22,23]. The time to development of malignant lymphoma against the background of Hashimoto's thyroiditis may vary in relation to histologic type. The reason for this difference remains unclear. However, some DLBCL patients might have transformed from MALT lymphoma after a relatively long time. In addition, the molecular mechanism linking chronic inflammation of thyroid lymphocytes to development of malignant lymphoma has not been clarified.

Genome-wide expression profile studies revealed that DLBCL patients had somatic mutations in multiple genes, including positive regulators of NF-κB, i.e., CARD 11, TRAF2, and TRAF5, among others, and negative regulators of *A20*[11,24]. No study of the *A20* mutation has enrolled a sufficient number of PTL patients, although Chanudet et al. showed that *A20* deletion was present in 1 of 9 patients with MALT lymphoma of the thyroid[17]. Wang et al. recently reported that Wnt5a and its receptor Ror2 might play a crucial role in the pathogenesis and progression of PTL[25]. We hypothesized that complex factors such as various gene mutations including *A20* abnormalities may be involved in PTL pathogenesis.

The most common coding polymorphism of *A20* was rs2230926 among the 32 types of polymorphism identified in sequencing experiments on autoimmune diseases

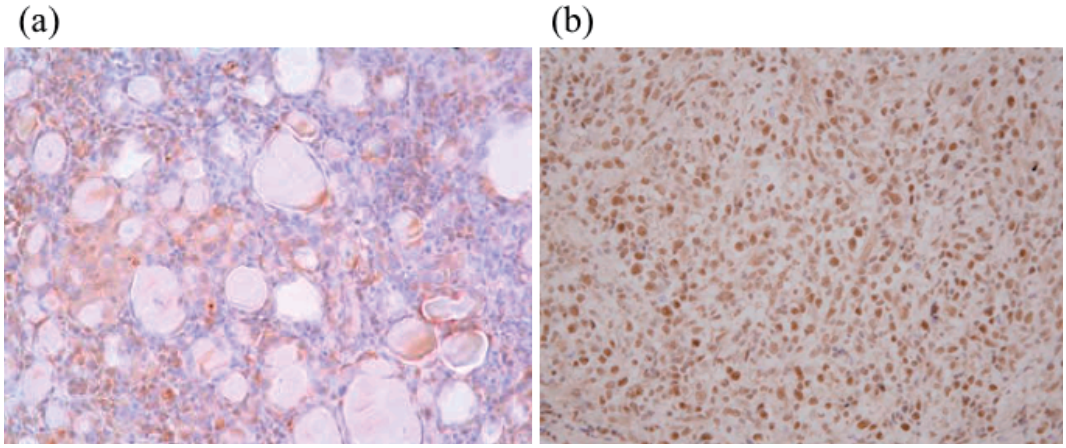

Fig. 2 Phosphorylated NF-κB p65 (Ser536) expression in normal thyroid (a) and lymphoma (b) tissue from a PTL patient (patient no. 1 in Table 3). Brown, immunostaining for phosphorylated NF-κB p65 with DAB; blue, counterstaining for nuclei with hematoxylin. Images are at 200× magnification.

such as RA, primary Sjögren's syndrome (pSS), Crohn's disease, and psoriasis[26]. Nocturne et al. reported that 77% of lymphoma patients with pSS had germline and/or somatic abnormalities of *A20*[20]. They also showed that the rs2230926 exonic variant was associated with increased risk of lymphoma in pSS patients but was not associated with onset of pSS in general[27]. Those results suggest that germline abnormalities of *A20* could lead to impaired control of NF-κB activation in B cells continuously stimulated by autoimmunity and thus increase the risk of lymphoma. Regarding *A20* abnormalities among patients with thyroid immune disease, Song et al. observed a clear association between polymorphisms of the *A20* gene and Grave's disease[28]. A study of A20 deletion in 383 cases found that 84 (21.9%) of 383 non-Hodgkin's lymphoma patients had 81 heterozygous losses but only 3 homozygous losses[16]. Other studies showed that *A20* mutations were significantly associated with *A20* heterozygous deletion[29,30] and that the mutations caused abnormal A20 protein expression and loss of function as well as homozygous deletion[30]. Activation of NF-κB promptly induces expression of A20 protein and normally suppresses excessive NF-κB activation, but in B cells in which A20 is inactivated because of these mutations, NF-κB is abnormally activated without suppression, and cell proliferation is promoted, thereby leading to tumorigenesis[29].

In our study, *A20* abnormalities were detected in 3 of 19 PTL patients (16%). Interestingly, they had a common missense variant in exon 3 (rs2230926 380T>G; F127C). Thus, *A20* abnormalities in PTL may be involved in the pathophysiology of lymphoma, as in other conditions. Furthermore, the *A20* abnormality was only detected in patients with Hashimoto's thyroiditis (20%). Our study showed that the rs2230926 mutation was associated with PTL in Hashimoto's thyroiditis patients but not with PTL in general. Furthermore, the *A20* mutation in tumor tissue was also detected in normal tissue in our patients. Notably, 1 patient (patient no. 3 in **Table 3**) had a heterozygous mutation in germline DNA but lost the wild-type allele in DNA of PTL tissue. This result indicates that a loss of heterozygosity may be associated with lymphoma pathogenesis. In contrast, 2 patients (nos. 1 and 2 in **Table 3**) had a heterozygous *A20* mutation in PTL tissue, and 1 (no. 1 in **Table 3**) had that mutation in normal tissue. Immunohistochemical study showed NF-κB activation in lymphoma tissue of a patient who had the *A20* mutation (no. 1 in **Table 3**) but not in normal thyroid tissues of the same patient (**Fig. 2**). Our preliminary results do not reveal whether there is a functional difference between heterozygous and homozygous *A20* mutations and their relationship to NF-κB activation in PTL. The *A20* mutation could play a role in the pathogenesis of PTL with Hashimoto's thyroiditis, caused by constitutive NF-κB activation in the thyroid gland.

We confirmed the histologic heterogeneity of PTL corresponding to differing clinical presentations and prognoses. *A20* abnormalities may be related to PTL pathogenesis in some patients. Future studies should attempt to clarify the pathogenesis, including *A20* abnormalities, of PTL and predict progression to lymphoma in patients with Hashimoto's thyroiditis.

Authors' contributions: T H designed this study. Y H and I M

supervised the experiments. T A performed pathological analysis. A T, O N, O-K A, and M K collected clinical data. I T, O H, T S, and Y N supervised the collection of clinical data.

Conflict of Interest: None declared.

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