

Prevalence and diagnostic challenges of thyroid lymphoma: a multi-institutional study in non-Western countries

Mitsuyoshi Hirokawa¹⁾, Ayana Suzuki¹⁾, Yuko Hashimoto²⁾, Shinya Satoh³⁾, Sule Canberk^{4),5)}, Jie Yang Jhuang⁶⁾, Chan Kwon Jung⁷⁾, Nichthida Tangnuntachai⁸⁾, Bozidar Kovacevic⁹⁾, Yun Zhu¹⁰⁾, Shipra Agarwal¹¹⁾ and Kennichi Kakudo¹²⁾

¹⁾ Department of Diagnostic Pathology and Cytology, Kuma Hospital, Kobe, Japan

²⁾ Department of Diagnostic Pathology, Fukushima Medical University School of Medicine, Fukushima, Japan

³⁾ Department of Endocrine Surgery, Yamashita Thyroid Hospital, Fukuoka, Japan

⁴⁾ Department of Pathology, Subdivision of Cytopathology, Acibadem University, Istanbul, Turkey

⁵⁾ Cancer Signaling & Metabolism, IPATIMUP/Instituto de Investigação e Inovação em Saúde, Universidade do Porto Rua Alfredo Allen, Porto, Portugal

⁶⁾ Department of Pathology, Mackay Memorial Hospital, Taipei, Taiwan

⁷⁾ Department of Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

⁸⁾ King Chulalongkorn Memorial Hospital, Bangkok, Thailand

⁹⁾ Institute of Pathology and Forensic Medicine, Military Medical Academy, Belgrade, Serbia

¹⁰⁾ Department of Pathology, Jiangsu Institute of Nuclear Medicine, Wuxi, China

¹¹⁾ Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

¹²⁾ Department of Pathology and Thyroid Disease Center, Izumi City General Hospital, Izumi, Japan

Abstract. Research on the primary thyroid lymphoma (PTL) diagnosis is limited, with only a few large sample size studies, reported from Asian countries. The aim of the present study was to clarify the current prevalence and challenges in PTL diagnosis, and recommended ancillary studies for PTL in non-Western countries. PTL ($n = 153$) cases were retrieved from 10 institutions in non-Western countries and analyzed. Ultrasound examination (UE) and fine needle aspiration cytology (FNAC) were used as main preoperative diagnostic tools in all participating institutions. Flow cytometry (FCM) was performed in the 5 institutions (50%). Lobectomy was the most common histological procedure to confirm the PTL diagnosis. All institutions routinely performed immuno-histochemical analysis. PTL was 0.54% of malignant thyroid tumor cases, with mucosa-associated lymphoid tissue lymphoma (MALTL) and diffuse large B-cell lymphoma (DLBCL) being 54.9% and 38.6%, respectively. Kuma Hospital, where the frequency of MALTL was highest (83.7%), routinely performed FCM using the materials obtained by FNAC. UE and FNAC sensitivities were 62.5% and 57.8%, respectively. In both UE and FNAC, sensitivity of MALTL was lower than of DLBCL. The study elucidated that the prevalence of PTL in non-Western countries was lower than previously reported. We propose that FCM should be more actively used to improve the preoperative diagnosis of MALTL. Our data predicted that the MALTL proportion will increase with improved diagnostic tools, while observation of PTL-suspected nodules without histological examination remains a viable option.

Key words: Thyroid, Lymphoma, Immunohistochemistry, Ancillary study, Aspiration cytology

PRIMARY THYROID LYMPHOMAS (PTLs) are rare, and most cases present as diffuse large B-cell lymphomas (DLBCLs), followed by mucosa-associated lymphoid tissue lymphomas (MALTLs) [1-11].

Due to the histological and cytological similarities between thyroid DLBCL and DLBCL arising from other organs, pathological diagnosis of thyroid DLBCL is a simple process. In contrast, diagnosis of thyroid MALTL is more complex, as there may be small-sized nodules, which may represent lymphoma cells of small or various sizes [12]. This subtype is occasionally confused with Hashimoto thyroiditis with high lymphocytic infiltration. The diagnosis is, therefore, made by a combination of histology

Submitted Apr. 8, 2020; Accepted Jun. 5, 2020 as EJ20-0202

Released online in J-STAGE as advance publication Jul. 9, 2020

Correspondence to: Mitsuyoshi Hirokawa, MD, PhD, FIAC, Department of Diagnostic Pathology and Cytology, Kuma Hospital, 8-2-35 Shimoyamate-dori, Chuo-Ku, Kobe, Hyogo 650-0011, Japan.

E-mail: mhirokawa@kuma-h.or.jp

and ancillary studies [12]. Additionally, MALTLs of the thyroid are cytogenetically different from MALTLs of other organs [13]. These factors lead to considerable inter-observer variability in the diagnosis of thyroid MALTLs.

Most of the reports on the diagnosis of PTL are sporadic, and studies using a large sample size are few, particularly in Asian countries. A multi-institutional study on PTL was proposed by The Asian Working Group in Thyroid Cytology (TAWGTC) network [14]. The current study is based on data compiled from 10 institutions in non-Western countries. The aim of this report was to clarify the current prevalence and diagnostic challenges of PTL, and recommended ancillary studies for PTL in non-Western countries.

Materials and Methods

TAWGTC proposed the current study on PTL and recruited the participating institutions. The eligibility for participation was to have an experience diagnosing at least 5 PTL cases over the last decade. PTL was defined as a lymphoma involving only the thyroid, or the thyroid and its adjacent lymph nodes (stages IE or IIE, respectively, under the Ann Arbor staging system). In the latter

cases, the thyroid lesions were larger than or appeared before those in the lymph nodes. Dissemination to the other organs was excluded by clinical evaluation, ultrasound examination (UE), PET/CT imaging, and/or bone marrow biopsy. One case with stage IV lymphoma was considered as PTL because the thyroid lesion was the first to appear. A questionnaire on PTL diagnosis was distributed. Ten institutions in non-Western countries were selected to participate: 1) Kuma Hospital (Japan), 2) Fukushima Medical University School of Medicine (Japan), 3) Yamashita Thyroid Hospital (Japan), 4) Acibadem University (Turkey), 5) Mackay Memorial Hospital (Taiwan), 6) The Catholic University of Korea (Korea), 7) King Chulalongkorn Memorial Hospital (Thailand), 8) Military Medical Academy (Serbia), 9) Jiangsu Institution of Nuclear Medicine (China), and 10) All India Institute of Medical Sciences (India). Annual malignant thyroid tumor cases from each institution ranged from 57 to 1,326 cases (Table 1). The institutions were classified into two groups, high (>500 malignant thyroid surgical cases/yr) and low (<500 cases/yr) volume centers. In total, 153 PTL cases were retrieved from the 10 institutions, and the diagnostic significance and challenges were examined.

Table 1 Prevalence of thyroid lymphoma in 10 participating institutions

Participants	Sources		Period	Surgical thyroid cases (47,339)	Malignant thyroid tumor cases (28,168) (/yr)	Lymphomas				
	Institutions	City, Country				Total	MALT	DLBCL	FL	Others*
A Suzuki, A & Hirokawa, M	Kuma Hospital	Kobe, Japan	2015.1–2017.12	4,902	2,926 (975)	43 (1.5%)	36	7	0	0
B Hashimoto, Y	Fukushima Medical University	Fukushima, Japan	2003.1–2019.7	1,750	916 (57)	28 (3.1%)	9	19	0	0
C Sato, S & Kakudo, K	Yamashita Thyroid Hospital	Fukuoka, Japan	2013.10–2018.12	4,382	2,556 (511)	30 (1.2%)	22	7	0	1
D Canberk, S	Acibadem University & IPATIMUP	Istanbul, Turkey & Port, Portugal	2009.5–2019.5	10,884	6,934 (630)	9 (0.1%)	1	5	2	1
E Jhuang, JY	Mackay Memorial Hospital	Taipei, Taiwan	2009.1–2019.6	805	753 (68)	6 (0.8%)	2	3	0	1
F Jung, CK	Catholic University of Korea & St. Mary's Hospital Seoul	Seoul, Korea	2013.1–2015.12	2,643	2,507 (836)	6 (0.2%)	1	4	0	1
G Tangnuntachai, N	King Chulalongkorn Memorial Hospital	Bangkok, Thailand	2009.1–2019.1	6,248	2,019 (202)	7 (0.3%)	2	4	0	1
H Kovacevic, B	Military Medical Academy	Belgrade, Serbia	2013.1–2018.12	1,829	909 (152)	5 (0.6%)	3	1	0	1
I Yun, Z	Jiangsu Institution of Nuclear Medicine	Wuxi, China	2013.1–2018.12	12,431	7,958 (1,326)	8 (0.1%)	5	2	1	0
J Agarwal, S	All India Institute of Medical Sciences	New Delhi, India	2009.1–2015.3	1,465	690 (115)	11 (1.6%)	3	7	0	1

DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; MALT, Mucosa-associated lymphoid tissue lymphoma.

* Burkitt, Mantle zone, Anaplastic large T cell, Hodgkin, and Unclassified lymphomas, and Plasmacytoma.

Statistical analyses were performed using the Stat Flex v.6 statistical software (Artech Co., Ltd, Osaka, Japan). Values of $p < 0.05$ were regarded as statistically significant in the Fisher probability test and Student's t -test.

Results

Prevalence

Of the 28,168 thyroid malignant tumors histologically diagnosed in the 10 participating institutions, 153 (0.54%) were PTL (Table 1). The incidence in each institution ranged from 0.1% to 3.1%; 4 institutions (40%) had an incidence rate of less than 0.5%. The incident rates were not related to the volume of thyroid malignant cases at the institutions. All of the Japanese and Indian institutions exhibited high incidence rates (more than 1%). Among PTLs, 84 cases (54.9%) were MALTL, followed by DLBCL (59 cases, 38.6%). The predominance of MALTL was seen in 4 institutions (2 Japanese, 1 Serbian and 1 Chinese institutions), 3 of which were high volume centers; Kuma Hospital, Japan had the highest incidence of MALTL (83.7%). The remaining lymphomas included 3 follicular lymphomas, 1 Burkitt lymphoma, 1 mantle zone lymphoma, 1 anaplastic large T cell lymphoma, 1 Hodgkin lymphoma, 1 plasmacytoma, and 2 unclassified lymphomas. In 129 cases with preoperative examination of Hashimoto thyroiditis-related autoantibodies, 108 (83.7%) were positive. The frequency in MALTL cases was higher than that in DLBCL cases (91.0% versus 75.6%).

Preoperative diagnosis

In addition to histological examination, diagnostic modalities included UE, fine needle aspiration cytology (FNAC), and flow cytometry (FCM). UE and FNAC were used as main preoperative diagnostic tools in all participating institutions (Table 2). FCM was performed in the 5 institutions (50%). Among them, only Kuma Hospital, where the frequency of MALTL was the highest,

routinely performed FCM using samples obtained by FNAC. The other four institutions occasionally or rarely performed FCM. The remaining 5 institutions did not perform FCM. Table 3 shows the results of the original preoperative UE reports. The frequencies of benign, intermediate, and high suspicion were 19.5%, 18.0%, and 62.5% respectively. The sensitivity of DLBCLs (86.4%) was significantly higher than that of MALTLs (48.1%) ($p < 0.05$). Of 77 MALTLs, 19 (24.7%) were interpreted as benign. Both sensitivity (61.4%) and false-negative rate (27.3%) of UE in small volume centers tended to be higher than those in high volume centers (52.4% and 15.5%, respectively); however, these differences were not statistically significant. Table 4 shows the results of the original preoperative FNAC reports. Of 116 PTLs with FNAC, 67 (57.8%) were reported as suspicious for malignancy or malignant. Sensitivities of MALTL and DLBCL were 45.2% and 76.9%, respectively. MALTLs reported as benign and atypia of undetermined significance (AUS), were 20.5% and 31.5%, respectively. Once more, both sensitivity (61.5%) and false-negative rate (17.9%) of FNAC in small volume centers tended to be higher than those in high volume centers (55.8% and 13.0%, respectively); however, these differences were not statistically significant. In 4 institutions (40%), observation without histological examination of PTL-suspected nodules was an available option.

Histological diagnosis

To confirm the diagnosis of lymphoma, histological examination was required by all institutions. Lobectomy was the most common procedure (Table 2). One institution did not perform core needle biopsies, because it was difficult to distinguish early stage MALTL from Hashimoto thyroiditis with high lymphocytic infiltration, and ancillary studies were limited. For large-sized lesions or DLBCL-suspected lesions, core needle biopsy or open biopsy were often indicated. Based on the questionnaire,

Table 2 Diagnostic procedures for thyroid lymphoma-suspected cases in 10 participating institutions

	Often to Always*	Occasionally to Sometimes**	Never to Rarely***
Ultrasound	10	0	0
Cytology	9	1	0
Flow cytometry	1	4	5
Histological examinations			
Core needle biopsy	3	6	1
Open biopsy	1	6	3
Lobectomy	6	2	2
Thyroidectomy	3	5	2

*; 60–100%, **; 30–60%, ***; 0–30%

Table 3 Preoperative ultrasound reports for 128 thyroid lymphoma cases

	Benign	Borderline	Suspicious for malignancy or Malignant
MALT (77)	19 (24.7%)	21 (27.3%)	37 (48.1%)
DLBCL (44)	5 (11.4%)	1 (2.3%)	38 (86.4%)
FL (3)	0 (0%)	1 (33.3%)	2 (66.7%)
Others (4)	1 (25.0%)	0 (0%)	3 (75.0%)
Total (128)	25 (19.5%)	23 (18.0%)	80 (62.5%)

DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; MALT, Mucosa-associated lymphoid tissue lymphoma.

Table 4 Preoperative cytological reports for 116 thyroid lymphoma cases

	ND/UNS	Benign	AUS/FLUS	FN/SFN	SFM & Malignant
MALTL (73)	1 (1.4%)	15 (20.5%)	23 (31.5%)	1 (1.4%)	33 (45.2%)
DLBCL (39)	3 (7.7%)	2 (5.1%)	4 (10.3%)	0 (0%)	30 (76.9%)
Others (4)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)
Total (116)	4 (3.4%)	17 (14.7%)	27 (23.3%)	1 (0.9%)	67 (57.8%)

AUS/FLUS, Atypia of undetermined significance or follicular lesion of undetermined significance; DLBCL, Diffuse large B-cell lymphoma; FN/SFN, Follicular neoplasm or suspicious for a follicular neoplasm; MALTL, Mucosa-associated lymphoid tissue lymphoma; ND/UNS, Nondiagnostic or Unsatisfactory; SFM, Suspicious for malignancy.

the most reliable pathological findings for diagnosing PTL were monotonous lymphocytic proliferation (nodular lesions consisting only of lymphocytes without epithelial cells) and lymphoepithelial lesions, followed by packing and follicular colonization. Extrathyroidal extension was not significant. There was consensus that the above findings were useful in distinguishing MALTL from Hashimoto thyroiditis. The presence of the follicles composed of Hürthle cells permeated by small lymphocytes indicated Hashimoto thyroiditis. In contrast, the follicular cells composing lymphoepithelial lesions and packing seen in lymphoma were not Hürthle cells. Large-sized lymphoma cells (more than 3 times the size of small lymphocytes), mitosis, apoptotic cells, no follicular cells, necrosis, and high Ki-67 labeling index favor DLBCL rather than MALTL. The term “plasmacytoma” was not used for thyroid. It was difficult to distinguish between MALTL with prominent plasmacytic differentiation from plasmacytoma, because cases with pure plasma cell proliferation can also display similar histological features of MALTL, including packing, lymphoepithelial lesions, and follicular colonization.

Ancillary studies

An immunohistochemical study using various antibodies was performed by all institutions and B-cell markers, T-cell markers, and follicular dendritic cell markers were used (Table 5). Follicular dendritic cell markers, such as CD21, CD23, and CD35, were used to

detect the disappearance of follicular dendritic cell meshwork, indicating follicular colonization. To determine light chain restriction, antibodies for kappa and lambda were used in 9 institutions (90%). Cytokeratins were used to highlight lymphoepithelial lesions and packing in 9 institutions (90%). In 6 institutions (60%), the Hans' classification was performed for DLBCLs. From the 40 DLBCLs examined by this method, 19 and 21 were the germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes, respectively. FCM based on CD45 and side scatter-based gating, IgH rearrangement analysis using southern blotting, and karyotypic analysis (G-banding chromosomal examination) were done in 5, 3, and 3 institutions, respectively.

Discussion

PTLs represent approximately 0.4 to 5% of all thyroid malignant tumors according to reports from Western countries [1-11]. In the present study, we showed that the incidence of PTLs in 10 non-Western participating institutions was 0.54%. The incidence in each institution ranged between 0.1% to 3.1%, and 4 institutions (40%) reported incidences of less than 0.5%. This demonstrated that the incidence of PTLs in non-Western countries may be lower than in the Western countries. The geographic variation in the incidence of lymphoma has previously been shown in the literature to be higher in the Western countries, and lower in Asia and Africa [15]. With the

Table 5 Ancillary studies for diagnosing thyroid lymphoma, performed in 10 participating institutions

Immunohistochemical study	
B-cell markers	(10) CD10 (10), CD19 (1), CD20 (10), CD79a (5), CD138 (1), PAX5 (2)
Immunoglobulins	(9) Light chain (9), Heavy chain (3)
T-cell markers	(10) CD3 (9), CD5 (9), UCHL1 (1)
Follicular dendritic cell markers	(10) CD21 (3), CD23 (6), CD35 (1)
Others	CD30 (5), CD43 (5), BCL2 (6), BCL6 (4), MUM1 (3), EBER (3), Cyclin D1 (4)
Epithelial marker (Cytokeratin)	(9)
Proliferation marker (Ki-67)	(3)
Flow cytometry	(5)
IgH rearrangement	(3)
Karyotypic examinations	(3)
FISH, chromosome 3	(1)

current study, our group demonstrated that PTLs followed the same trend.

Hashimoto thyroiditis is considered a risk factor of PTLs, especially MALTL. More than 90% of patients with PTL have elevated circulating thyroidal autoantibodies [16]. In the current study, 83.7% of PTL cases revealed Hashimoto thyroiditis-related autoantibodies. As expected, the frequency in MALTL cases was higher than that in DLBCL cases (91.0% and 75.6%, respectively).

Almost all PTLs are from the B-cell lineage, and several reports have described that DLBCL was the most common subtype (>60%), followed by MALTL (10–30%) and FL (2–10%) [1–11]. In the current study, however, the predominant subtype was MALTL, and the highest rate of incidence among the institutions was 83.7%. Three of four institutions with MALTL predominance were high volume centers. As DLBCLs frequently contain the components of MALTL, they are speculated to be transformed from pre-existing MALTLs [6]. The cause could be due to earlier detection of MALTLs by improved diagnostic accuracies of the UE, FNAC, and ancillary studies [12, 13]. In fact, a recent trend indicated towards an increasing proportion of MALTL [12, 13, 17]. However, the possible involvement of racial and/or environmental factors cannot be ruled out.

UE is the primary imaging modality used to detect PTL, and typically shows 3 patterns: nodular, diffuse, and mixed [18]. UE was used as a main preoperative diagnostic tool in all participating institutions. Hirokawa *et al.* reported 32 PTL cases with UE, and the sensitivity was 62.5% [12]. In our samples, the sensitivity was 62.5%. The sensitivity of MALTL (48.1%) was lower than that of DLBCL (86.4%). Of MALTL cases, 24.7% were interpreted as benign. The early and accurate detection of MALTL using UE should be addressed in future studies.

The next step in diagnosing PTL is to perform FNAC. In 9 of 10 institutions, FNAC was performed as the main diagnostic tool. The remaining institute preferred core needle biopsy rather than FNAC. According to the review of 593 PTL cases by Zhang *et al.*, the sensitivity of FNAC was 48.0% [19]. In our samples, the sensitivity was 57.8%. Of the MALTL cases, 20.5% were classified as benign, since MALTL is composed of heterogeneous cells and may be confused with Hashimoto thyroiditis with high lymphoid proliferation. In addition, MALTL is usually associated with Hashimoto thyroiditis. The diagnosis of DLBCL is simpler due to the presence of large monotonous atypical cells. The diagnostic accuracy of FNAC for PTL significantly depended on the proportion of MALTL and DLBCL cases in the samples. According to the Bethesda system, when PTL is suspected in FNAC, a repeat aspirate for FCM is recommended [20]. The pre-operative FCM using aspirated materials has the same diagnostic accuracy as using resected materials [13]. Stacchini *et al.* reported that the combination of cytology and FCM showed sensitivity and specificity of 100% [21]. Among our participating institutions, the one where the proportion of MALTL was the highest preoperatively performed FCM using the aspirated materials from all lymphoma suspected nodules [12]. We propose that FCM should be more actively used to improve the preoperative diagnosis of MALTL.

A histological examination was generally performed for suspected PTL nodules from the FNAC. In our series, a lobectomy was the most common procedure. For large-sized or DLBCL-suspected lesions, a core needle biopsy or open biopsy might be indicated. One institution did not perform core needle biopsies, because it was difficult to distinguish early stage MALTL from Hashimoto thyroiditis with high lymphocytic infiltration, and ancillary studies were limited. Therefore, there is a possibility that

histological examination by core needle biopsy may overlook early stage MALTL.

To confirm the diagnosis of PTL, immunohistochemical testing is necessary [10]. Monotonous lymphocytic proliferation is demonstrated by solid proliferation of lymphoid cells expressing B-cell marker (CD20). For lymphoma with plasma cell differentiation, the demonstration of light chain restriction using antibodies against kappa and lambda is useful [22]. Cytokeratins were used to highlight lymphoepithelial lesion and packing. Follicular dendritic cell markers, either CD21 or CD23, were used to demonstrate follicular colonization in most of the institutions. Hans' classification markers, such as BCL6 and MUM1, were used by 30% of the institutions. Thus, the minimum required immunohistochemical panel to diagnose PTL should include B-cell markers, T-cell markers, light chains, cytokeratins, and follicular dendritic cell markers.

Other ancillary studies, including FCM, IgH rearrangement, and karyotypic analyses, may provide important information for the diagnosis, classification and biological behaviors of lymphomas [12, 13, 20]. Suzuki *et al.* examined 110 PTL cases and reported that the positive rates of light chain restriction, heavy chain DNA rearrangement, and chromosomal abnormalities were 69.2%, 65.4%, and 49.0%, respectively [13]. The negative rate for all three studies was 3.8%. Although the ancillary studies were useful and should be adopted more actively, their utilization was not common in non-Western countries.

Spontaneous regression of PTL has rarely been reported [23, 24]. Nakao *et al.* reported that 12 of 22 hypoechoic thyroid lesions that were possibly PTLs based on UE and FNAC, decreased in size or disappeared during careful observation [25]. Thus, observation without histological diagnostic procedures can be considered an option for PTL-suspected nodules. This approach was adopted by 4 (2 Japanese, 1 Thai, and 1 Chinese institutions) of 10 institutions. We expect that the indication for and significance of careful observation of PTL-suspected nodules will be established in the future.

Conclusion

The cause that the predominant subtype was MALTL

could be due to earlier detection of MALTLs by improved diagnostic accuracies of the UE, FNAC, and ancillary studies. We demonstrated that the incidence of PTLs in non-Western countries may be lower than in the Western countries. The early and accurate detection of MALTL using UE should be addressed in future studies. We propose that FCM should be more actively used to improve the preoperative diagnosis of MALTL. The minimum required immunohistochemical panel to diagnose PTL should include B-cell markers, T-cell markers, light chains, cytokeratins, and follicular dendritic cell markers. Although the ancillary studies were useful and should be adopted more actively, their utilization was not common in non-Western countries. We expect that the indication for and significance of careful observation of PTL-suspected nodules will be established in the future.

Acknowledgement

The authors wish to thank Dr. Akira Miyauchi, Department of Surgery, Kuma Hospital, for commenting a draft of this manuscript.

Statement of Ethics

No ethical approval was obtained because this study did not involve a prospective evaluation or laboratory animals, and only involved non-invasive procedures.

Disclosure Statement

The authors have no disclosures to make. No funding was received for this study.

Author Contributions

Conceptualization and methodology: M. Hirokawa; Case presentation and questionnaire responses: All authors; Data processing: A. Suzuki; Original draft preparation and writing: M. Hirokawa; Draft review and editing: A. Suzuki; Supervision: K. Kakudo.

References

1. Sharma A, Jasim S, Reading CC, Ristow KM, Villasboas Bisneto JC, *et al.* (2016) Clinical presentation and diagnostic challenges of thyroid lymphoma: a cohort study. *Thyroid* 26: 1061–1067.
2. Adhikari LJ, Reynolds JP, Wakely PE Jr (2016) Multi-institutional study of fine-needle aspiration for thyroid lymphoma. *J Am Soc Cytopathol* 5: 170–176.
3. Noble VV, Ermann DA, Griffin EK, Silberstein PT (2019)

- Primary thyroid lymphoma: an analysis of the National Cancer Database. *Cureus* 11: e4088.
4. Pavlidis ET, Pavlidis TE (2019) A Review of primary thyroid lymphoma: molecular factors, diagnosis and management. *J Invest Surg* 32: 137–142.
 5. Walsh S, Lowery AJ, Evoy D, McDermott EW, Prichard RS (2013) Thyroid lymphoma: recent advances in diagnosis and optimal management strategies. *Oncologist* 18: 994–1003.
 6. Stein SA, Wartofsky L (2013) Primary thyroid lymphoma: a clinical review. *J Clin Endocrinol Metab* 98: 3131–3138.
 7. Mehta K, Liu C, Raad RA, Mitnick R, Gu P, *et al.* (2015) Thyroid lymphoma: a case report and literature review. *World J Otorhinolaryngol* 5: 82–89.
 8. Kakkar A, Purkait S, Agarwal S, Mallick S, Gogia A, *et al.* (2019) Primary thyroid lymphoma: a series from a tertiary care center in Northern India. *J Cancer Res Ther* 15: 669–675.
 9. Widder S, Pasiaka JL (2004) Primary thyroid lymphomas. *Curr Treat Options Oncol* 5: 307–313.
 10. Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS, *et al.* (2000) Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *Am J Surg Pathol* 24: 623–639.
 11. Nam M, Shin JH, Han BK, Ko EY, Ko ES, *et al.* (2012) Thyroid lymphoma: correlation of radiologic and pathologic features. *J Ultrasound Med* 31: 589–594.
 12. Hirokawa M, Kudo T, Ota H, Suzuki A, Kobayashi K, *et al.* (2017) Preoperative diagnostic algorithm of primary thyroid lymphoma using ultrasound, aspiration cytology, and flow cytometry. *Endocr J* 64: 859–865.
 13. Suzuki A, Hirokawa M, Higashiyama T, Fukata S, Takada N, *et al.* (2019) Flow cytometric, gene rearrangement, and karyotypic analyses of 110 cases of primary thyroid lymphoma: a single-institutional experience in Japan. *Endocr J* 66: 1083–1091.
 14. Bychkov A, Kakudo K, Hong S (2017) Current practices of thyroid fine-needle aspiration in Asia: a missing voice. *J Pathol Transl Med* 51: 517–520.
 15. Huh J (2012) Epidemiologic overview of malignant lymphoma. *Korean J Hematol* 47: 92–104.
 16. Noureldine SI, Tufano RP (2015) Association of Hashimoto's thyroiditis and thyroid cancer. *Curr Opin Oncol* 27: 21–25.
 17. Watanabe N, Noh JY, Narimatsu H, Takeuchi K, Yamaguchi T, *et al.* (2011) Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24553 patients with Hashimoto's disease. *Br J Haematol* 153: 236–243.
 18. Ota H, Ito Y, Matsuzuka F, Kuma S, Fukata S, *et al.* (2006) Usefulness of ultrasonography for diagnosis of malignant lymphoma of the thyroid. *Thyroid* 16: 983–987.
 19. Zhang L, Castellana M, Virili C, Crescenzi A, Giorgino F, *et al.* (2018) Fine-needle aspiration to diagnose primary thyroid lymphoma: a systematic review and meta-analysis. *Eur J Endocrinol* EJE-18-0672.R1. doi: 10.1530/EJE-18-0672.
 20. Cibas ES, Ali SZ (2017) The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid* 27: 1341–1346.
 21. Stacchini A, Pacchioni D, Demurtas A, Aliberti S, Cassenti A, *et al.* (2015) Utility of flow cytometry as ancillary study to improve the cytologic diagnosis of thyroid lymphomas. *Cytometry B Clin Cytom* 88: 320–329.
 22. Kojima M, Shimizu K, Shimizu K, Masawa N (2009) Incidental MALT type lymphoma exhibiting prominent plasma cell differentiation associated with Hashimoto's thyroiditis. A two case report. *Head Neck Pathol* 3: 27–30.
 23. Illán-Gambín F, Manresa-Manresa P, Rodríguez-Aleo E, Aranda-López I (2020) Spontaneous regression of primary thyroid lymphoma: two rarities at the same time. *Türk Patoloji Derg* 36: 164–168.
 24. Uohashi A, Imoto S, Matsui T, Murayama T, Okimura Y, *et al.* (1996) Spontaneous regression of diffuse large-cell lymphoma associated with Hashimoto's thyroiditis. *Am J Hematol* 53: 201–202.
 25. Nakao T, Nishikawa M, Hisakado M, Kasahara T, Kudo T, *et al.* (2018) Characteristics and natural course of hypoechoic thyroid lesions diagnosed as possible thyroid lymphomas by fine needle aspiration cytology. *Thyroid Res* 11: 8.