Review Article on Asian and Western Practice in Thyroid Pathology: Similarities and Differences

Thyroid lymphoproliferative lesions in Asia

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Contributions: (I) Conception and design: S Agarwal; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: T Nakra; (V) Data analysis and interpretation: T Nakra, S Agarwal; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Primary thyroid lymphomas (PTLs) are rare and most commonly present as rapidly enlarging thyroid mass causing obstructive symptoms. Due to worldwide differences in clinical practices related to thyroid malignancy, this review was conducted to compare the clinicopathological and diagnostic modalities related to PTL and their similarities and differences between the Asian and Western countries. Using the search engine PubMed, published data on thyroid lymphomas was collected and reviewed. A total of 18 Asian and 22 Western studies were included. Most of PTLs were B-cell Non-Hodgkin lymphomas (NHL). While mucosa-associated lymphoid tissue (MALT) lymphoma was the commonest (41.1%) among Asians, diffuse large B cell lymphoma (DLBCL) (71.9%) predominated in the Western population. Some rare subtypes of PTL were also identified. Majority of all patients in Asian as well as Western studies presented with early stage (stage I/II) disease. Interestingly, when compared with Asian patients, a larger proportion of patients from the West presented with higher stage (stage III/IV) disease (12.2% *vs.* 3%). Ultrasonography (USG) and fine needle aspiration cytology (FNAC) in addition to histological examination usually by core needle biopsy and in some by open procedures were used for the diagnosis of PTL in both the cohorts. The various ancillary techniques used were immunocytochemistry (ICC), flowcytometry (FC), immunohistochemistry (IHC), and molecular testing. The use of ancillary techniques for PTL diagnosis was more common in the West compared to Asia and markedly increased the sensitivity of cytology to diagnose PTL. Treatment and prognosis largely depend upon the subtype of PTL and stage at presentation. To conclude, from the available published literature, there is an apparent difference between Asian and Western cohorts in the histological type and stage of presentation of PTL, but the results may be affected by publication and selection bias. Also, advanced ancillary techniques are more commonly adopted in the West.

Keywords: Asia; cytology; flowcytometry (FC); immunocytochemistry (ICC); thyroid lymphoma; West

Submitted Apr 01, 2020. Accepted for publication Jul 04, 2020.
doi: 10.21037/gs-20-432
View this article at: http://dx.doi.org/10.21037/gs-20-432

Introduction

Primary lymphomas of thyroid are rare and account for 1–5% of all thyroid malignancies (1) and 1–2% of extra-nodal lymphomas (2). Primary thyroid lymphoma (PTL) is defined as a lymphoma which involves the thyroid gland with or without the involvement of regional neck lymph nodes; but without the contiguous spread or distant metastases from other areas of involvement at the time of diagnosis (3). These are more common in females and present in sixth to seventh decades of life (4). Although the normal thyroid gland is devoid of any native lymphoid tissue PTL often arises in a background of Hashimoto thyroiditis (HT) with the relative risk of 67 as compared to those without thyroiditis (5). The chronic antigenic stimulation leads to accumulation of genetic abnormalities and proliferation of abnormal B-cell clones giving rise to lymphoma (1). Most of the PTLs are Non-Hodgkin

lymphomas (NHL) of B-cell type with diffuse large B-cell lymphoma (DLBCL) being the most common subtype followed by mucosa-associated lymphoid tissue (MALT) lymphoma (4). Ultrasonography (USG) is usually the initial modality for the diagnosis of thyroid lesions. However, pathological confirmation and subtyping of lymphoma is essential. Fine needle aspiration cytology (FNAC) is a useful, effective and well-established technique for evaluation of thyroid swellings. But low sensitivity of FNAC for detecting thyroid lymphoma questions its diagnostic accuracy especially for MALT lymphoma where distinction from HT may be challenging. Since PTLs are sensitive to chemotherapy and radiotherapy, accurate diagnosis using minimally invasive tools is crucial to obviate the need for unnecessary resections and allow for early treatment. The use of ancillary techniques for immunophenotyping using immunohistochemistry (IHC)/immunocytochemistry (ICC)/flow cytometry (FC) can greatly aid in diagnosing difficult cases (6). Various studies have been published in literature addressing the diagnostic issues related to thyroid lymphomas. Herein we review all the available data regarding the clinicopathological characteristics, methods used for the diagnosis and treatment of PTL. The main focus of this review is comparison of diagnostic approach and practices being followed by the Asian and Western countries in management of PTL.

Methods

An internet-based literature search was conducted for the published work on PTL using PUBMED. All the original articles pertaining to both histology and cytology where full text was available were reviewed. Case reports, case series, review articles, and conference proceedings were excluded. Cross references of the included studies were also checked for additional studies. In case of more than one study from the same institute with overlapping time period, and possibility of overlapping data, study with larger cohort was included. The cytology results wherever available including their category as per 'The Bethesda system for reporting thyroid cytopathology' (TBSRTC) were recorded (7). Prevalence of specific PTL subtypes was calculated as a proportion of number of cases of that subtype reported in literature to the total number of PTL cases reported. The prevalence of patients in a particular clinical stage was also calculated similarly. Data from studies which were limited to a specific subtype of PTLs was excluded from final analysis to calculate proportions.

Results and discussion

A total of 40 studies fulfilled the inclusion and the exclusion criteria, detailing 2,928 PTL cases (*Table 1*) including some studies which were based on specific subtypes of PTL (17,39,44).

Clinical presentation

Clinical presentation was similar across Asian and Western studies. The most common (75–85%) presenting symptom of PTL is rapidly growing thyroid mass (19,23,38,46), and can mimic anaplastic thyroid carcinoma (47). Other symptoms include hoarseness of voice, dysphagia, dyspnea or stridor as a result of compression due to mass (48). Presence of neck lymphadenopathy is variable. A proportion of patients (5–20%) may also present with B-symptoms like fever, night sweats and weight loss (18,28,42). A history of HT may be there as risk of developing PTL is 40–80 times higher in these patients (48). In a study by Mizokami *et al.*, all 9 patients of HT developed MALT lymphoma during 3–18 years of USG follow up (15).

The staging of PTL is based on Ann Arbor staging criteria similar to staging of other lymphomas (47). The reported data in literature (wherever available) regarding the staging of PTL from Asian and Western cohorts, has been depicted and compared in *Table 2*.

While most cases (97% in Asia and 87.8% in West) presented as either stage I or stage II disease, a smaller proportion (3% in Asia and 12.2% in West) had stage III or stage IV disease. The apparent difference in proportion of patients presenting in higher stage in West may be attributed to the proportion of DLBCL cases in the Western cohort (71.9% in West *vs.* 37.3% in Asia).

Prevalence and spectrum/classification of PTL

Reported prevalence of PTL was similar in Asian (11,12) and Western studies (27,28,30,34,35) (*Table 2*). MALT lymphoma and DLBCL are the most common histological subtypes of PTL (*Table 2*). Interestingly, of all the PTLs, while DLBCL was the most frequent (71.9%; including DLBCL transformed from low-grade NHL) subtype in western literature, MALT lymphoma was the commonest (41.1%) in Asian studies. Some recent studies have subclassified DLBCL into germinal and post-germinal center type (12,14,18,26). Other rare subtypes of PTL reported include follicular lymphoma (FL), chronic

Table 1 Review of published literature on thyroid lymphomas

Asian *vs.* Western studies	Countries	Authors, year	Study period	Number of cases
Asian studies	China	Wu *et al.*, 2016 (8)	1992–2015	10
		Yang *et al.*, 2015 (9)	1995–2012	12
		Sun *et al.*, 2010 (10)	1991–2007	40
		Lam *et al.,*1999 (11)	1968–1997	23
	India	Kakkar *et al.*, 2019 (12)	2009 –2015	11
		Gupta *et al.*, 2005 (13)	1998–2004	10
	Japan	Suzuki *et al.*, 2019 (14)	2012–2017	110
		Mizokami *et al.*, 2016 (15)	2005–2014	9
		Kaba *et al.*, 2015 (16)	2007–2010	101
		Yoshida *et al.*, 2013 (17)	2002–2011	6
		Watanabe *et al.*, 2011 (18)	1994–2004	171
		Matsuzuka *et al.*, 1993 (19)	1963–1990	119
		Ota *et al.*, 2006 (20)	2000–2004	170
	Korea	Chai *et al.*, 2015 (21)	2000–2013	38
		Nam *et al.*, 2012 (22)	1995–2010	13
		Hwang *et al.*, 2009 (23)	1991–2006	44
		Kwak *et al.*, 2007 (24)	2003–2005	6
	Malaysia	Sarinah *et al.*, 2010 (25)	1998–2006	17
Western studies	Canada	Moshynska *et al.*, 2008 (26)	1995–2000	12
		Morgen *et al.*, 2010 (6)	1988–2009	9
	Denmark	Pedersen & Pedersen, 1996 (27)	1983–1991	50
	France	Thieblemont *et al.*, 2002 (28)	1987–2000	26
	Italy	Stacchini *et al.*, 2015 (29)	2001–2013	13
		Sangalli *et al.*, 2001 (30)	1980–1998	17
	Poland	Czopnik *et al.*, 2017 (31)	2007– 2015	10
	Serbia	Colovic *et al.*, 2007 (32)	1994–1999	9
	Spain	Lerma *et al.*, 2003 (33)	1992–2001	12
	Turkey	Bostanci *et al.*, 2017 (34)	2009–2015	11
	UK	Alzouebi *et al.*, 2012 (35)	1970–2010	70
		Penney *et al.*, 2011 (36)	1992–2004	35
		Hyjek *et al.*, 1988 (37)	1957–1987	15
	USA	Sharma *et al.*, 2016 (38)	2000–2014	75
		Quesada *et al.*, 2016 (39)	2000–2015	7
		Adhikari *et al.*, 2016 (40)	2000–2013	68
		Boonyaarunnate *et al.*, 2013 (41)	1993–2012	13

Table 1 (*continued*)

Table 1 (*continued*)

Asian *vs.* Western studies	Countries	Authors, year	Study period	Number of cases
		Graff-Baker *et al.*, 2009 (42)	1973–2005	1408
		Ruggiero *et al.*, 2005 (43)	1977–2004	22
		Wang *et al.*, 2005 (44)	1990–2005	5
		Cha *et al.*, 2002 (45)	1985–2000	23
		Derringer *et al.*, 2000 (46)	1985–1993	108

lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (40,42), Burkitt lymphoma (BL) (39), mantle cell lymphoma (MCL) (42), Hodgkin lymphoma (HL) (44), plasmacytoma (42) and NHL of T-cell origin (17,38) (*Table 2*).

Diagnostic modalities

Imaging

USG, although not specific, is the initial modality of choice for the screening of thyroid masses. The USG findings in PTL are mostly based on internal echoes, border of the lesion and posterior echoes. These features classify the lesions detected on USG into nodular type, diffuse type and mixed type as observed in many studies (9,15,20). In all these types, it has been found that PTLs are predominantly hypoechoic masses (9,22) and show enhancement of posterior echoes (9,20). These hypoechoic areas correspond to lymphoepithelial lesions of PTL (22). The positive predictive value (PPV) of detecting lymphoma is 63–65% in cases of nodular or mixed type and these can mimic follicular lesion or adenomatous goiter. However diffuse type is difficult to differentiate from chronic thyroiditis where around 62% cases can be misdiagnosed as PTL (20). USG has been used as a pre-treatment modality in PTL management in both Asian and Western studies.

FNAC

FNAC is a valuable and widely accepted diagnostic tool for evaluating thyroid masses. The use of TBSRTC is recommended for categorizing thyroid cytology worldwide however, in thyroid lymphoma cases except for one Asian study (12), none of the studies have used TBSRTC for categorizing aspirates. This observation may be attributed to the reason that most of these studies were conducted before the introduction of TBSRTC.

In a recent study from Japan, of the 107 patients of MALT lymphoma, 79% cases could be diagnosed as thyroid lymphoma by FNAC (2). In other Asian studies dealing with smaller number of cases, the diagnostic rate of thyroid lymphoma on FNAC was 50–90% (10,13,23,24). Interestingly, none of the nine cases in the study by Wu *et al.* could be diagnosed as NHL on cytology, and this was attributed to the lack of adequate experience of cytopathologists for the diagnosis of rare diseases (8). In contrast to DLBCL, false negative rates are high among MALT lymphoma or low-grade NHL which can be misdiagnosed as lymphocytic thyroiditis because of the presence of large numbers of heterogeneous cells and the concurrent presence of HT or due to sampling error (48). Selective aspiration of reactive lymphoid follicles of HT may be misinterpreted as "atypical lymphoid cells", as also reported in two studies (2,40), but none of them reported it as "suspicious for" or "diagnostic of" lymphoma. Liquid-based cytology (LBC) smears were prepared in three of the Western studies (6,40,44) and in none of the included Asian studies. A study from Asia compared the cytomorphology of PTL on LBC with that of conventional smears. This study was not included in the analysis in this review because of overlapping study period with another study published from the same institute (14). The authors reported that on LBC large elongated swollen nuclei act as a clue to differentiate PTL from non-neoplastic lymphoid cells and that lymphoglandular bodies are not reliable for diagnosing PTL (49).

Although studies from both Asia and West have documented the utility of FNAC in initial evaluation of PTL (*Table 3*), the diagnostic rate in West was 65–100% (6,29,30,38,40), similar to that reported in Asian studies (6,19,29,30,40,45).

Surgical biopsies

FNAC can be used for definite diagnosis or suggesting

Table 2 Prevalence and clinicopathological distribution of primary thyroid lymphomas

Parameters	Asian studies	Western studies
Prevalence of PTL	2% of thyroid malignancies and 0.4% all lymphomas (11,12)	2.3–3.5% of thyroid malignancies and 2.1–2.6% of all lymphomas (27,28,30,34,35)
Histological subtypes (%)		
MALT lymphoma	41.10	12.40
DLBCL	32.90	66.00
Mixed lymphomas (MALT lymphoma /FL with DLBCL)	4.40	5.90
FL	1	7.90
CLL	–	2.50
BL	–	0.20
MCL	–	0.05
Plasmacytoma	0.30	0.80
HL	–	1.90
NHL-HG	2.80	0.75
NHL-IG	11.50	–
NHL-LG	3.80	0.70
B-NHL	0.10	0.60
PTLL	0.10	–
PTCL NOS	0.30	0.20
NK/T	–	0.10
ALCL	1.70	–
Stage at presentation (%)		
I	45.70	57.50
II	51.30	30.30
III	0.90	2.80
IV	2.10	9.40

PTL, Primary thyroid lymphoma; MALT, Mucosa-associated lymphoid tissue; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; BL, Burkitt lymphoma; MCL, mantle cell lymphoma; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; HG, high grade; IG, intermediate grade; LG, low grade; PTLL, primary T-cell lymphoblastic lymphoma; PTCL NOS, primary T-cell lymphoma, not otherwise specified; NK/T, NK/T cell lymphoma; ALCL, anaplastic large cell lymphoma.

a diagnosis of PTL, but confirmation and subtyping requires tissue biopsy, core needle biopsy (CNB) being the most common modality. In lymphomas per se CNB can successfully classify histological subtypes in 89.7% of neck lymphomas (50). For PTL, CNB has shown an overall sensitivity of 87–93% compared to 50–71% with FNAC (38,51). CNB has been proven to be superior predominantly in diagnosing MALT lymphoma and has 100% sensitivity compared to lower sensitivity of FNAC (25%) (38). The accurate diagnosis and exact characterization of PTL using CNB can avoid unnecessary surgical interventions.

Open surgical procedures (wedge biopsy/resection) were also performed in some studies (6,8,10,12-15,22-25,27, 30-32,34-36,38,41-46). The reasons for this procedure varied from non-diagnostic CNB results (8,25) or served as a therapeutic/debulking procedure or to relieve obstructive symptoms or associated pain (10,22,25,31,35,38). On evaluating corresponding available cytology details of these

Table 3 Number and percentage of studies where use of pretreatment modalities and ancillary techniques for diagnosis of thyroid lymphoma has been elaborated

Ancillary techniques	Asian studies (18)	Western studies (22)
Fine needle aspiration cytology	16 (88.9)	16 (72.7)
Liquid-based cytology	0	3 (13.6)
Immunocytochemistry		
Cell blocks	0	3 (13.6)
Smears	2 (11.1)	2 (9.1)
Immunohistochemistry	4 (22.2)	8 (36.4)
Flowcytometry	3 (16.7)	7 (31.8)
Molecular testing		
PCR for gene rearrangement	1 (5.6)	4 (18.2)
Cytogenetics	2(11.1)	3 (13.6)
Southern blot	2(11.1)	0
EBER-ISH	1 (5.6)	2 (9.1)
FISH	0	1 (4.5)

Data present as n (%). EBER-ISH, Epstein-Barr encoding region-in situ hybridization; FISH, fluorescence in-situ hybridization; PCR, polymerase chain reaction.

cases (6,8,10,12,13,15,22-25,30-32,34,38,41,43-45), it was found that the cytological spectrum encompassed the entire spectrum of TBSRTC categories including one case of follicular neoplasm (25).

Ancillary techniques

ICC is helpful for diagnosis and subtyping of PTL using cytology material. Limited ICC can be performed on cytology smears. Although some studies used LBC for cytological evaluation (6,40,44), none of the studies have specified use of LBC for ICC. Cell blocks (CB) permit application of a more extensive ICC panel, and are particularly popular in the Western countries (*Table 3*). Even a basic panel of CD 3 and CD 20 performed on CB has been reported to be useful in diagnosing PTL (29,30,40). Using this limited panel, Sangalli *et al.*, in 2001, could correctly identify NHL in 90% of their cases; one case showed T-cell predominance and was labeled as HT. This false negative case was attributed to sampling error as MALT lymphoma along with HT was confirmed on follow-up thyroidectomy specimen (30). Stacchini *et al.*, also used ICC on CB. Of the 13 cases, 11 could be diagnosed as NHL and two cases were called suspicious for NHL (29). No such data of ICC on CB has been reported from Asia, though there are studies in which ICC was performed on cytology smears for PTL diagnosis (10,13).

Immunohistochemistry is commonly applied on surgical biopsy or on specimen of thyroidectomy, if resected; the advantage being the elaborate panel which can be applied due to more available tissue. Its utility and results have been documented both in Asian (9,11,12,18) and Western studies (26-28,32,39,43,44,46).

Flowcytometry (FC) is a reliable method for evaluation of patients suspected to have PTL. The National Cancer Institute (NCI)-sponsored Thyroid Fine Needle Aspiration State of the Science Conference concluded that FC is useful for immunophenotyping of clinically suspected cases of PTL (52), as has also been documented in some Asian and Western studies (14,15,17,28,29,39-41,43,45). Hirokawa *et al.* tried to establish a diagnostic algorithm based on findings of USG, FNAC and FC. They aimed at identifying monoclonal population of lymphoid cells with light chain restriction by CD45 gating using FC and defined it as κ/λ light chain ratios of greater than 3:1 or less than 1:3. They found that 25% cases of PTL were missed and nearly 11% cases of HT showed light chain restriction. But still the sensitivity and specificity of FC (75% and 88.4%) was much more than FNAC alone (59.4% and 41.9%) (53). Mizokami

et al. used FC for assessment of monoclonality (15). Another study focused on Primary peripheral T-cell lymphoma (PTCL) of thyroid also used FC, however further details have not been provided in the published work (17).

Of the western studies, an extensive panel of antibodies was used for immunophenotyping in two (29,41), while the other three studies (39,40,45) used a limited panel of B/T- cell along with light chains. The remaining two studies (28,43) did not discuss the panel of antibodies used in FC analysis.

Cha *et al.* compared the diagnostic rate of FNA in pre and post era of immunophenotyping and found that FC significantly impacted the ability to correctly identify lymphoma on FNAC (45). FC can increase sensitivity and specificity of cytology to diagnose PTL to 100% (29) obviating the need for a diagnostic surgical biopsy (41,45).

Cytology sample obtained by FNA is the most commonly used material for FC, and was used by most authors. Tissue samples obtained by trucut biopsy, wedge biopsy or thyroidectomy may also be used. As the cells need to be suspended in liquid medium, additional processing is required for tissue specimens, like homogenization of sample, which is more time consuming and labour intensive; and can result in reduction of viable cells. Thus, FNAC samples are considered superior to tissue specimens for FC analysis. However, resection specimens provide the advantage of histologic correlation which is lacking with FNA (54). Two studies, one from the USA (43) and the other from Japan (14) have documented use of tissue samples in FC for PTL management. While the former used frozen specimens for FC (43), the latter have just mentioned resection specimens as the material used (14). Suzuki *et al.* performed FC on a large number of aspirated and resected materials and found nearly similar detection rates (73.7% and 69.2% respectively) of light chain restriction from both types of materials (14).

Molecular testing: use of molecular methods as an ancillary technique in PTL diagnosis and management has also been discussed in some studies (11,14,15,17,26,28,29,39,40,43,44,46), more commonly in those from the West (*Table 3*). Majority of these methods were performed from surgical tissue specimens except two studies where FNA material was used (29,40).

Polymerase chain reaction (PCR) has also been used in PTL for assessment of monoclonality or identification of gene rearrangement (15,26,29,40,43). A rare case of primary T-cell lymphoblastic lymphoma diagnosed on FC was confirmed by identification of T-cell receptor (TCR) rearrangement without undergoing biopsy (29). In another study, IgH gene sequences were analyzed to test the hypothesis of PTL arising in a background of HT (26).

Cytogenetic analysis for characteristic translocations have been used in rare subtypes of PTL like t(8;14) in BL, t(14;18) in FL and t(11;14) in MCL, all documented in Western literature (28,40,46). A study from Asia reported karyotypic analysis using G-banding chromosomal examination and documented chromosomal aberrations in 49.0% of PTLs including abnormalities like addition, trisomy, and deletions besides translocations. The unique observation by these authors was that none of the MALT lymphoma cases showed any of the four translocations t(1;14)(p22;q32), t(11;18)(q21;q21), t(14;18)(q32;q21), and t(3;14)(p14;q32) known to be associated with MALT lymphomas. They suggested that this discrepancy may be due to cytogenetic differences between MALT lymphomas arising in the thyroid and other organs (14). However, a recent study from Germany documented presence of t(11;18)(q21;q21) in one of the two low grade thyroid MALT lymphomas evaluated by cytogenetics. The second case harbored multiple aberrations. Four cases of high-grade MALT lymphoma were also analyzed, and showed complex chromosomal clones (55). Another study from Austria demonstrated presence of t(3;14)(p14;q32) in 3 of the 6 cases of thyroid MALT lymphoma assessed (56).

Cytogenetic analysis has also been used to detect genetic alterations in PTCL-NOS of thyroid (17). Yoshida *et al.* studied six cases of PTCL-NOS associated with autoimmune thyroiditis, and found loss of 6q24·2 in four. None showed genomic alterations previously reported for PTCL-NOS. The authors, hence, suggested that primary PTCL-NOS of the thyroid arising from autoimmune thyroiditis may be a distinct entity among PTCL-NOS (17).

Southern blot analysis for molecular testing was used in two Asian studies to detect TCR gene rearrangement in PTCL, NOS involving the thyroid gland (17) and to assess IgH rearrangement in PTLs (14), respectively. The incidence of IgH rearrangement documented in the latter study was lower in MALT lymphoma (58.1%) compared to DLBCL and FL (100%) (14).

The association between EBV and lymphomas is well-known, but still its detection for diagnostic reasons in PTL is uncommon, due to rarity of EBV-associated BL and HL in thyroid. One of the studies from China has analyzed EBV gene expression using in-situ hybridization (ISH) and IHC against EBV-LMP1, EBNA-2 and ZEBRA

protein (11). Among the 19 thyroid lymphomas tested in this study, one primary DLBCL and one secondary BL were found to be positive with EBER-ISH. However, in two studies from USA, EBER-ISH was used for diagnostic workup in cases of BL and HL (39,44). One of these two studies also used fluorescence *in-situ* hybridization for the detection of *MYC* gene rearrangement in BL (39). Similar data is lacking from Asian studies.

Treatment and prognosis

Histology and stage of the tumor play an important role in deciding management protocol, the latter being similar across the World. The role of surgery in PTL has declined in the recent years and is limited mostly as palliative measure in patients presenting with obstructive symptoms (10,22,25,31,35,38,48). Although optimal management of PTL is still controversial, multimodality treatment is considered as treatment of choice. For localized indolent lymphomas like MALT or FL, locoregional control of disease is achieved by either surgery or radiotherapy alone or in combination (47). For aggressive or disseminated PTLs, combination of chemotherapy and radiotherapy has been proven to be effective for control of disease and improving the outcome (35). The standard regimen of chemotherapy is a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The 5-year overall survival rate ranges from 35% to 100% (35). MALT lymphoma and DLBCL of thyroid gland have been reported to have better prognosis and survival rates when compared to other extra-nodal and nodal sites (2,57).

Limitations of the study

Considering the retrospective nature, presence of publication and selection bias is contemplated.

Conclusions

PTLs are rare malignancies. They have a similar clinical presentation across the World, though the available literature hinted towards a larger proportion of cases in the Western cohort presenting with diffuse large B cell lymphoma as well as higher stage disease. These results, however, may be impacted by publication and selection bias. Although pre-treatment USG and aspiration cytology are routinely used worldwide as routine screening and diagnostic measures, ancillary techniques like LBC, immunocytochemistry, FC and molecular analysis, are much more commonly used in the West.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Kennichi Kakudo) for the series "Asian and Western Practice in Thyroid Pathology: Similarities and Differences" published in Gland Surgery. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Peer Review File: Available at http://dx.doi.org/10.21037/gs-20-432

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-432). The series "Asian and Western Practice in Thyroid Pathology: Similarities and Differences" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Nakra T, Jain D, Agarwal S. Thyroid lymphoproliferative lesions in Asia. Gland Surg 2020;9(5):1827-1837. doi: 10.21037/gs-20-432