Hashimoto Thyroiditis in Primary Thyroid Non-Hodgkin Lymphoma

A Systematic Review and Meta-Analysis

Antonio Travaglino, MD,[1] Mirella Pace, MD,[1] Silvia Varricchio, BTD, PhD,[1] Luigi Insabato, MD, PhD,[1] Claudia Giordano, MD,[2] Marco Picardi, MD, PhD,[2] Fabrizio Pane, MD, PhD,[2] Stefania Staibano, MD, PhD,[1] and Massimo Mascolo, MD, PhD[1]

From the [1]Department of Advanced Biomedical Sciences, Pathology Section, and [2]Department of Clinical Medicine and Surgery, Hematology Section, University of Naples "Federico II," Naples, Italy.

Key Words: Thyroid; Lymphoma; MALT; Hashimoto; Thyroiditis

Am J Clin Pathol 2019;XX:0–0

DOI: 10.1093/AJCP/AQZ145

ABSTRACT

Objectives: *To assess the prevalence of Hashimoto thyroiditis (HT) in primary thyroid lymphoma (PTL) and whether it differs between mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL).*

Methods: *Electronic databases were searched for studies assessing HT prevalence in PTL, based on antithyroid antibodies, clinical history, or pathology. Pooled prevalence of HT and its association with histotype (MALT or DLBCL) were calculated.*

Results: *Thirty-eight studies with 1,346 PTLs were included. Pooled prevalence results were 78.9% (any HT evidence), 65.3% (antithyroid antibodies), 41.7% (clinical history), and 64% (pathology). HT prevalence was significantly higher in MALT lymphoma than in DLBCL (*P = *.007) and in mixed DLBCL/MALT than in pure DLBCL (*P = *.002).*

Conclusions: *Overall, 78.9% of patients with PTL have any HT evidence, but only half of these had been clinically followed. The difference in HT prevalence suggests that a subset of DLBCL may not derive from MALT lymphoma.*

Primary thyroid lymphoma (PTL) is a rare malignancy that accounts for 1% to 5% of all thyroid malignancies and 1% to 7% of all extranodal lymphomas.[1-4] PTL occurs preferentially in females, with an incidence peak in the seventh decade.[1,4,5] The most common clinical presentation of PTL is a palpable mass in the neck, which may cause dysphagia, dyspnea, and hoarseness. In addition, B symptoms (fever, night sweats, and weight loss of 10% and higher in the past 6 months) can be present.[1]

The most common histotypes are diffuse large B-cell lymphoma (DLBCL), which accounts for 50% to 70% of cases, and mucosa-associated lymphoid tissue (MALT) lymphoma, which accounts for 10% to 50% of cases.[6] Follicular lymphoma, small lymphocytic lymphoma, Burkitt lymphoma, mantle cell lymphoma, T-cell lymphoma, and Hodgkin lymphoma have been described less commonly.[1]

The most important risk factor for PTL is Hashimoto thyroiditis (HT), which causes a 40- to 80-fold increase in the risk of PTL.[3] However, it is unclear whether HT is a necessary condition for the development of PTL. In fact, while some authors suggested that all PTLs originate in an HT setting, other authors reported no evidence of HT in a series of patients with PTL.[2,3,7-9] Moreover, it is also unclear whether HT is associated with particular PTL histotypes more strongly than with other ones.

Aims of this study were (1) to define the prevalence of HT in patients with PTL, based on the several different

diagnostic criteria adopted (eg, positive antithyroid antibodies, clinical history, histologic evidence) and (2) to assess the association of HT with PTL histotypes.

Materials and Methods

Methods of this review followed those from previous studies.[10,11] The study methods were defined before the beginning of the study. All stages of the review were performed independently by three authors (A.T., M.P., and M.M.). Disagreements were resolved by consensus among authors. The study was reported by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12]

Search Strategy and Study Selection

Six electronic databases (MEDLINE, Scopus, Web of Sciences, OVID, Cochrane Library, and Google Scholar) were searched from January 2009 to December 2018 for studies assessing the presence of HT in patients with PTL. The following combination of text words was used: (primary OR primitive) AND thyroid AND lymphoma. Exclusion criteria were as follows: data not extractable, inclusion of only T-cell PTLs, inclusion of only Hodgkin PTL, language other than English, case reports, and reviews.

Data Extraction

Data were not modified during extraction. Primary extracted data were the number of patients with HT and the total number of patients with PTL. The variable "number of patients with HT" was categorized based on the methods for HT diagnosis as follows: presence of antithyroid antibodies, clinical history of HT, histologic evidence of HT, and overall prevalence of HT diagnosed by any method.

The variable "total number of patients with PTL" was also categorized based on the histologic type of lymphoma as follows: MALT or DLBCL. Moreover, wherever possible, data on DLBCL were subdivided into DLBCL with the MALT-type component and pure DLBCL.

Risk of Bias Within Study Assessment

A modified version of the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)[13] was used to assess the risk of bias within studies. Four domains related to the risk of bias were assessed: (1) patient selection (ie, if the patients were selected consecutively or if at least inclusion criteria and period of enrollment were reported), (2) HT diagnosis ("index test" in the original QUADAS-2; ie, if methods for HT diagnosis were clearly described, (3) PTL diagnosis ("reference standard" in the original QUADAS-2; ie, if the results were subdivided according to the histotype of PTL), and (4) flow (ie, if all PTLs were assessed for the presence of HT). Authors' judgments were categorized as "low risk," "high risk," or "unclear risk of bias," as previously described.[14,15] Concerns about applicability were also assessed for the "patient selection" domain (ie, if methods for patient selection did not suit the aim of our review, regardless of their correctness).

Data Analysis

The prevalence of HT in PTL was calculated as the number of patients diagnosed with HT by the total number of PTL patients. A subgroup analysis was also performed based on the time of publication (until 2010 or after 2010). The association of HT with the PTL histotype was assessed by using the odds ratio (OR). Both HT prevalence and OR were calculated for each study and as a pooled estimate with a 95% confidence interval (CI), as well as reported graphically on forest plots. The random-effect model of DerSimonian-Laird was used to pool data. Statistical heterogeneity was quantified by using Higgins's inconsistency index (I^2) and categorized as null ($I^2 = 0\%$), minimal ($0 < I^2 \leq 25\%$), low ($25\% < I^2 \leq 50\%$), moderate ($50\% < I^2 \leq 75\%$), or high ($I^2 > 75\%$), as previously described.[16,17]

Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014) and Comprehensive Meta-Analysis (Biostat) were used for the analyses.

Results

Study Selection and Characteristics

Thirty-eight studies[1-3,6-9,18-28] with a total of 1,346 PTLs were included, while 21 studies were excluded (inclusion of only T-cell PTL or only Hodgkin PTL; unavailability of data on HT). The process of study selection is reported in Supplementary Figure 1 (all supplemental materials can be found at *American Journal of Clinical Pathology* online). The diagnosis of HT was performed based on clinical history in 14 studies, on antithyroid antibodies in 15 studies, on histologic features in 12 studies, and on sonographic features in two studies. In 16 studies, HT diagnosis was based on the presence of at least one criterion among several ones. Characteristics of the included studies are reported in **Table 1**.[1-3,6-8,18-48] Data about HT subdivided according to each diagnostic criterion are reported in Supplementary Table 1.

DOI: 10.1093/AJCP/AQZ145

Table 1
General Characteristics of the Included Studies

Study	Country	Period of Enrollment	Sample Size, No.
1999 Lam et al[18]	Hong Kong	1968-1997	23
2000 Derringer et al[3]	United States	1985-1993	107
2001 Belal et al[19]	Arabia	1975-1995	52
2002 Thieblemont et al[20]	France	1987-2000	26
2003 Kim et al[21]	Korea	1994-2001	9
2003 Lerma et al[22]	Spain	1992-2001	7
2005 Gupta et al[23]	India	1998-2004	10
2006 Cho et al[24]	Korea	1989-2004	18
2006 Sato et al[25]	Japan	1989-2004	58
2007 Colović et al[26]	Serbia	1994-1999	9
2007 Niitsu et al[27]	Japan	1998-2005	32
2007 Au et al[9]	China	1992-2002	9
2008 Moshynska and Saxena[28]	Canada	1995-2000	20
2009 Avenia et al[29]	Italy	1986-2008	6
2009 Hwang et al[30]	Korea	1991-2006	44
2010 Sun et al[31]	China	1991-2007	40
2011 Lee et al[32]	Korea	1997-2007	7
2011 Mian et al[33]	Multicenter	1985-2006	48
2011 Onal et al[34]	Multicenter	1986-2006	87
2011 Watanabe et al[35]	Japan	1990-2004	171
2012 Alzouebi et al[36]	United Kingdom	1970-2010	70
2012 Nam et al[37]	Korea	1995-2010	16
2012 Oh et al[38]	Korea	1989-2010	27
2013 Cha et al[39]	Korea	1994-2012	29
2013 Kumar et al[7]	India	2005-2010	16
2014 Ma et al[40]	China	2002-2008	39
2014 Watanabe et al[41]	Japan	2005-2011	43
2014 Xia et al[8]	China	1995-2010	27
2015 Chai et al[42]	Korea	2000-2013	38
2015 Knief et al[43]	Germany	Unclear	21
2015 Li et al[44]	China	2007-2014	27
2015 Wang et al[2]	China	2007-2013	13
2015 Wei et al[45]	China	2009-2012	20
2015 Yang et al[46]	China	1995-2012	12
2017 Bostancı et al[1]	Turkey	2009-2015	11
2017 Gu et al[47]	China	1999-2017	27
2018 Li et al[48]	China	2008-2017	20
2018 Watanabe et al[6]	Japan	1990-2009	107
Total			1,346

Risk of Bias Assessment

For the "patient selection" domain, one study was considered at unclear risk of bias (it was unclear whether patients were consecutively selected), while all the other studies were considered at low risk (all reported at least inclusion criteria and period of enrollment). Concerns about applicability were raised for eight studies (inclusion of only MALT,[6,32,38] only DLBCL,[27,33,35,43] only intermediate/high-grade PTLs[19]). For the "HT diagnosis" domain, the risk of bias was unclear for eight studies[7,26,34,37,38,41,47,48] (unclear methods for HT diagnosis) and low for all the remaining studies. For the "PTL diagnosis" domain, the risk of bias was unclear for 12 studies[2,19,22,23,31,34,36,37,40,44,45,47] (results not subdivided according to PTL histotype) and low for all the remaining studies. For the "flow" domain, the risk of bias was unclear for seven studies[22,28,31,33,37,39,44] (presence of HT not assessed on all PTLs) and low for all the remaining studies. Results of the risk of bias assessment are reported in Supplementary Figure 2.

HT Prevalence

Among patients with PTL, the overall prevalence of HT (ie, the presence of at least one among several different diagnostic criteria) was 78.8% (95% CI, 66%-87.7%; **Figure 1**), with high statistical heterogeneity among studies (I^2 = 83.530). The percentage of patients with positive antithyroid antibodies was 65.3% (95% CI, 52.3%-76.3%; **Figure 2**), with moderate heterogeneity (I^2 = 61.347%). The percentage of patients with a clinical history of HT was 41.7% (95% CI, 27.8%-57.1%; **Figure 3**), with high heterogeneity (I^2 = 76.481%). The percentage of patients with histologic evidence of HT was 64% (95% CI, 44.4%-79.8%; **Figure 4**), with high heterogeneity (I^2 = 87.878%).

DOI: 10.1093/AJCP/AQZ145

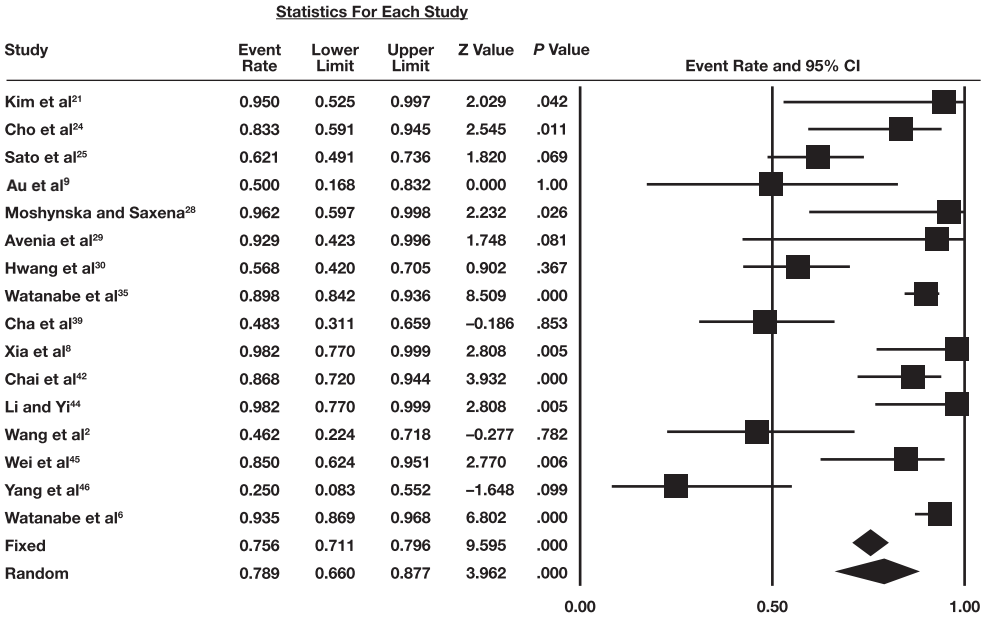

Figure 1 Forest plot reporting the prevalence of Hashimoto thyroiditis in patients with primary thyroid lymphoma based on the presence of any diagnostic criterion. CI, confidence interval.

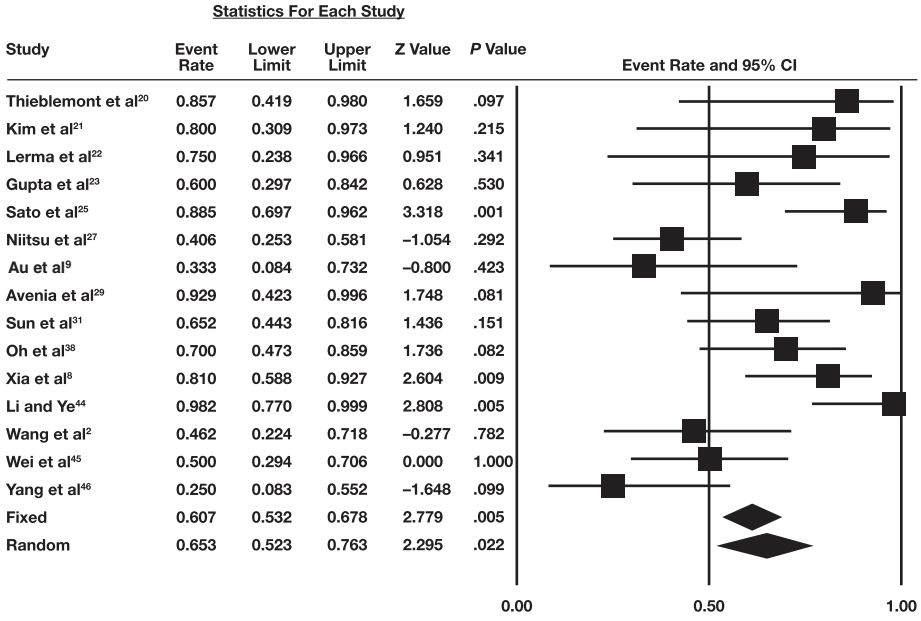

Figure 2 Forest plot reporting the prevalence of Hashimoto thyroiditis in patients with primary thyroid lymphoma based on the positivity for antithyroid antibodies. CI, confidence interval.

Subgroup Analysis

The overall prevalence of HT was 71% (95% CI, 55.8%-82.7%) in the studies published until 2010 and 82.8% (95% CI, 67.3%-91.8%) in the studies published after 2010 (Supplementary Figure 3). The percentage of patients with positive antithyroid antibodies was 67.9% (95% CI, 50.6%-81.3%) in the studies published until 2010 and 62.7% (95% CI, 40.4%-80.6%) in the studies published after 2010 (Supplementary Figure 4). The percentage of patients with a clinical history of HT was 51.1% (95% CI, 31.1%-70.8%) in the studies published until 2010 and 30.9% (95% CI, 15.2%-52.8%) in the studies published after 2010 (Supplementary Figure 5). The percentage of patients with histologic evidence of HT was 60.2% (95% CI, 37.6%-79.2%) in the studies published until 2010 and 73.1% (95% CI, 31.3%-94.2%) in the studies published after 2010 (Supplementary Figure 6).

DOI: 10.1093/AJCP/AQZ145

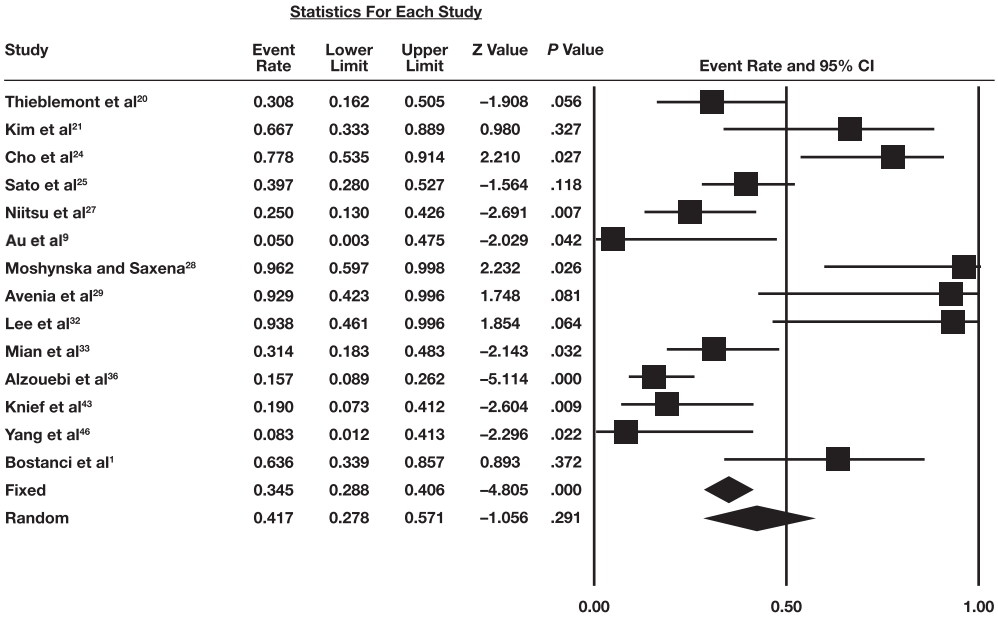

Figure 3 Forest plot reporting the prevalence of Hashimoto thyroiditis in patients with primary thyroid lymphoma based on the clinical history. CI, confidence interval.

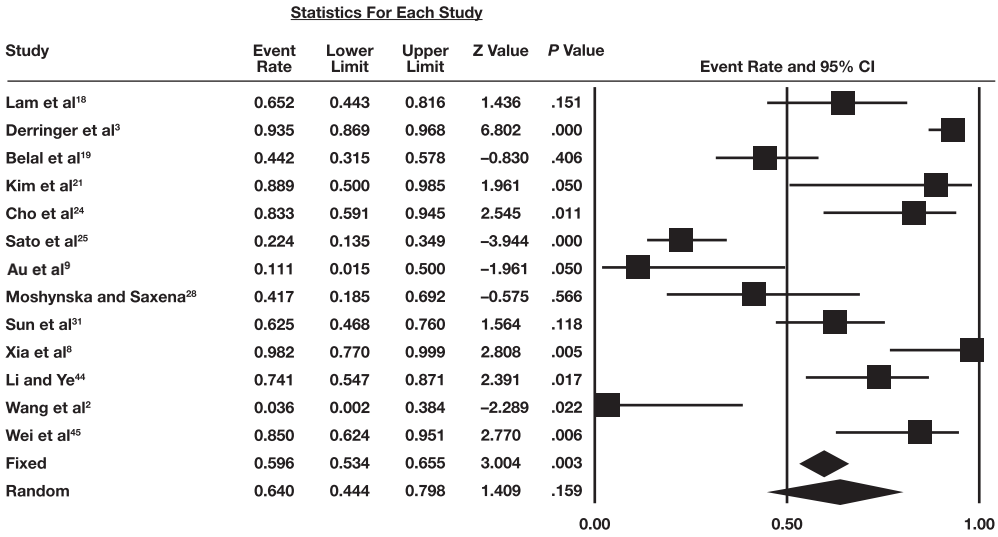

Figure 4 Forest plot reporting the prevalence of Hashimoto thyroiditis in patients with primary thyroid lymphoma based on the presence of histologic features. CI, confidence interval.

HT in PTL Histotypes

Among PTL, the prevalence of HT was significantly higher in MALT lymphoma than in DLBCL, with an OR of 2.175 (95% CI, 1.238-3.821; P = .007; Figure 5), with low statistical heterogeneity among studies (I^2 = 19.295%). Furthermore, among DLBCL, the prevalence of HT was significantly higher in DLBCLs with a MALT-type component than in pure DLBCLs, with an OR of 9.11 (95% CI, 2.313-35.879; P = .002; Figure 6), with null heterogeneity (I^2 = 0.000%).

Discussion

Main Findings and Interpretation

This study showed that, among patients with PTL, 65.3% had positive antithyroid antibodies, 41.7% had a clinical history of HT, 64% had histologic evidence of HT, and 78.9% had any evidence of HT. Furthermore, HT prevalence was significantly higher in MALT lymphoma than in DLBCL and in DLBCLs with a MALT-type component than in pure DLBCLs.

DOI: 10.1093/AJCP/AQZ145

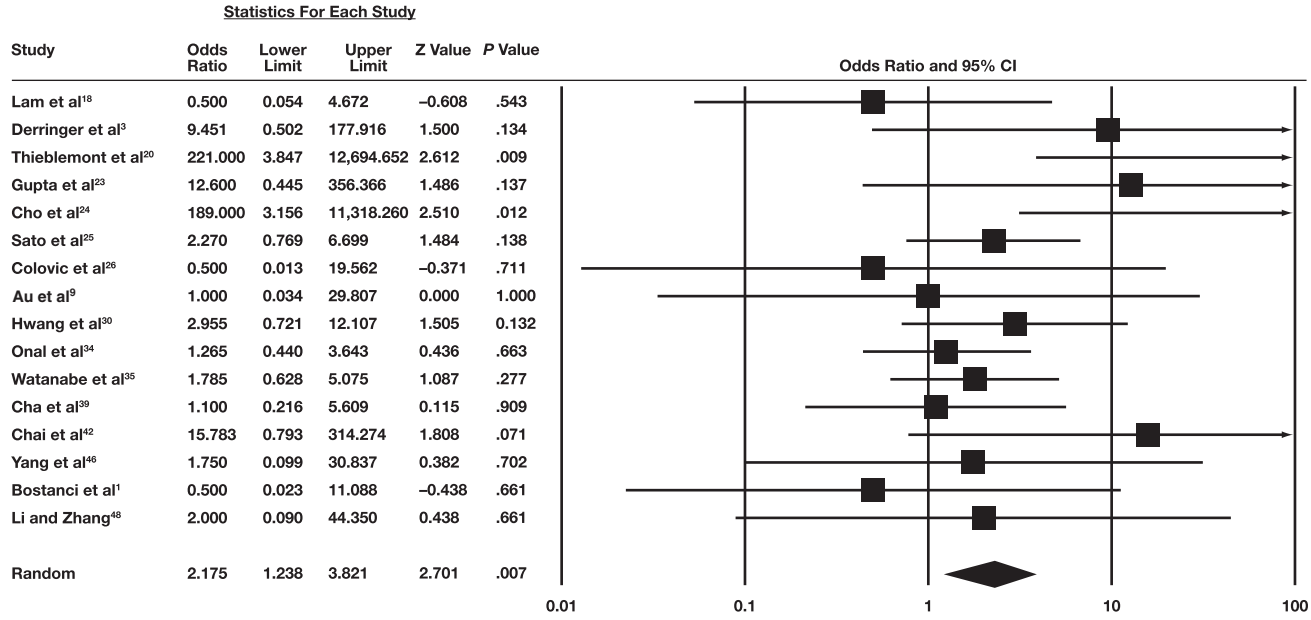

Figure 5 Forest plot reporting the odds ratio for the association of Hashimoto thyroiditis with mucosa-associated lymphoid tissue lymphoma. CI, confidence interval.

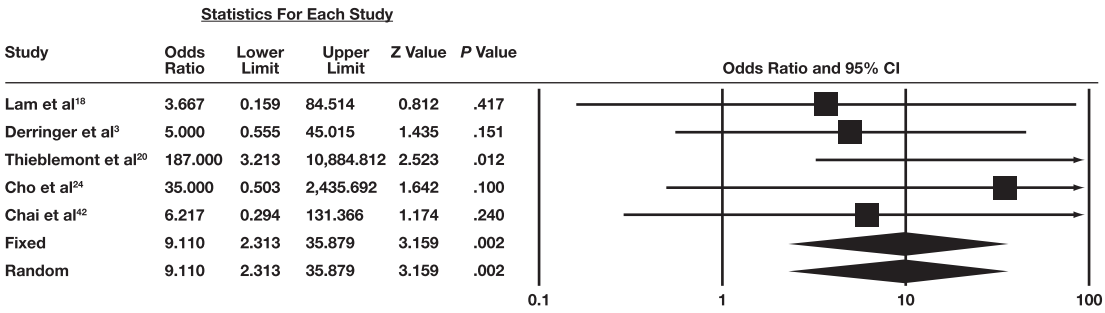

Figure 6 Forest plot reporting the odds ratio for the association of Hashimoto thyroiditis with the presence of a mucosa-associated lymphoid tissue component in diffuse large B-cell lymphoma. CI, confidence interval.

The diagnosis of HT is based on clinical features, serum antithyroid antibodies, sonographic features, and pathologic examination.

Clinical features include local manifestations due to mass effect and variable systemic manifestations due to hypothyroidism. The main antithyroid antibodies are antithyroperoxidase antibodies, which constitute the most reliable serologic marker of HT, and antithyroglobulin antibodies. Ultrasonographic features consist of a loss of echogenicity of the thyroid parenchyma, which appears similar to the surrounding muscles. A characteristic pathologic feature is the presence of an interstitial infiltrate, which is mainly constituted of lymphocytes organized into true lymphoid follicles.[49]

The association between HT and PTL is well established. Patients with HT bear a 40- to 80-fold increased risk of PTL. However, the prevalence of HT in patients with PTL is highly variable among the studies in the literature.[2,3,7-9] These differences might be due to the different methods used to ascertain the presence of HT. In fact, patients with HT not necessarily show all sign and symptoms of disease,[49] and thus it is possible that the prevalence may vary based on the criterion adopted for diagnosis.

Our results showed that the overall prevalence of HT in PTL was 78.9%. Diagnostic parameters suitable for the meta-analysis were presence of antithyroid antibodies, clinical history of HT, and histologic evidence of HT; unfortunately, only two studies adopted ultrasonographic criteria to diagnose HT,[8,40] not allowing a meta-analysis. As expected, the prevalence of HT according to each single parameter was lower than the overall prevalence. However, while the percentage of patients with antithyroid antibodies was similar to those with pathologic features of HT (65.3% and 64%, respectively), a clinical history

DOI: 10.1093/AJCP/AQZ145

of HT was definitely less common (41.7%). In the included studies, "clinical history of HT" included any past evidence that led to a diagnosis of HT. Our results indicate that about four-fifths of patients with PTL have a background of HT, but in half of these patients HT had not been diagnosed previously. It remains to be defined whether an improvement in thyroid screening programs may also improve prevention of PTL.[50,51]

In the subgroup analyses about time of publication, we found an increase of the overall prevalence of HT over time, which was also observed with regard to histologic features. On the other hand, a decrease was found for the percentage of patients with a clinical history of HT, while the percentage of patients with antithyroid antibodies appeared relatively stable. However, none of these differences was statistically significant, as indicated by the widely overlapping 95% CI. Furthermore, the period of enrollment of the studies did not reflect the time of publication; for example, the study by Gupta et al,[23] published in 2005, enrolled patients since 1998, while the newer study by Alzouebi et al,[36] published in 2012, enrolled patients since 1970. Therefore, it is unclear if these findings reflect a real variation in the prevalence of HT over time.

Regarding histotypes, PTL is in most cases a MALT lymphoma or a DLBCL. The association between marginal zone lymphomas and autoimmune disorders is well described. It is thought that the chronic stimulation of B cells caused by autoantigens leads to an increased risk of cumulative genetic events; the activation of the nuclear factor–κB pathway seems to be crucial in this process.[52] According to several authors, almost all cases of PTLs are MALT type, which arise from HT and can progress to DLBCL. Based on this hypothesis, PTL might be considered a single entity with a homogeneous etiopathogenesis.[25] In the stomach, clonal relationships and identical light chain restrictions were found in DLBCL and MALT lymphoma, suggesting that most if not all DLBCLs derive from an evolution of MALT lymphomas.[53,54] In the thyroid, such a hypothesis is also supported by the relatively common finding of a MALT-type component coexistent with DLBCL.[3,18,20,24,42] According to our results, among PTLs an HT background was significantly less common in DLBCL than in MALT lymphoma; furthermore, the prevalence of HT was significantly lower in pure DLBCL than in DLBCL with a MALT component. Such a finding may suggest that at least a part of primary thyroid DLBCL has an etiopathogenesis different from MALT lymphomas. A previous study found that VH immunoglobulin family usage was different between MALT lymphomas and DLBCL of the thyroid,[25] supporting the hypothesis of a different pathogenesis. Further studies are necessary in this regard.

Strengths and Limitations

To our knowledge, this is the first meta-analysis assessing the prevalence of HT in PTL. Furthermore, this may also be the first review that considered separately the different methods for diagnosing HT in this field.

The main limitation to our results might be the statistical heterogeneity among studies. This heterogeneity may in part be due to the different aims of the included studies. Some studies are in fact centered on pathology, while other ones are focused on clinical features, imaging techniques, or treatment outcomes. Although we tried to limit this heterogeneity by assessing separately the different diagnostic methods for HT, statistical heterogeneity remained significant.

The lack of definitive pathology specimens for many patients may be another limitation. The assessment of histologic features might indeed be inaccurate on small biopsy specimens. However, surgery is recommended only for low-grade lymphoma at stage IE-IIE, while high-grade lymphomas and advanced lymphomas are treated with chemo/radiotherapy.[55]

Finally, a subgroup analysis based on geographic differences was not feasible, due to the unbalanced geographic distribution of the included studies. In fact, most of the included studies were from East Asia, while only six were from Europe and only two from North America.

Conclusion

Among patients with PTL, 78.9% show any evidence of HT, 65.3% have positive antithyroid antibodies, 64% have histologic evidence of HT, and only 41.7% have a clinical history of HT. HT is significantly less common in DLBCL than in MALT lymphoma, suggesting that a subset of DLBCLs may not derive from MALT lymphomas.

Corresponding author: Antonio Travaglino, MD; antonio.travaglino.ap@gmail.com.

References

1. Bostancı H, Dikmen K, Akyürek N, et al. Eleven patients with primary thyroid lymphoma: a single center experience. *Turk J Med Sci.* 2017;47:1322-1327.
2. Wang Z, Fu B, Xiao Y, et al. Primary thyroid lymphoma has different sonographic and color Doppler features compared to nodular goiter. *J Ultrasound Med.* 2015;34:317-323.
3. Derringer GA, Thompson LD, Frommelt RA, et al. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *Am J Surg Pathol.* 2000;24:623-639.

DOI: 10.1093/AJCP/AQZ145

4. Widder S, Pasieka JL. Primary thyroid lymphomas. *Curr Treat Options Oncol.* 2004;5:307-313.
5. Cheng V, Brainard J, Nasr C. Co-occurrence of papillary thyroid carcinoma and primary lymphoma of the thyroid in a patient with long-standing Hashimoto's thyroiditis. *Thyroid.* 2012;22:647-650.
6. Watanabe N, Narimatsu H, Noh JY, et al. Long-term outcomes of 107 cases of primary thyroid mucosa-associated lymphoid tissue lymphoma at a single medical institution in Japan. *J Clin Endocrinol Metab.* 2018;103:732-739.
7. Kumar R, Khosla D, Kumar N, et al. Survival and failure outcomes in primary thyroid lymphomas: a single centre experience of combined modality approach. *J Thyroid Res.* 2013;2013:269034.
8. Xia Y, Wang L, Jiang Y, et al. Sonographic appearance of primary thyroid lymphoma-preliminary experience. *PLoS One.* 2014;9:e114080.
9. Au WY, Fung A, Ma ES, et al. HLA associations, microsatellite instability and epigenetic changes in thyroid lymphoma in Chinese. *Leuk Lymphoma.* 2007;48:531-534.
10. Raffone A, Travaglino A, Saccone G, et al. Management of women with atypical polypoid adenomyoma of the uterus: a quantitative systematic review. *Acta Obstet Gynecol Scand.* 2019;98:842-855.
11. Lionetti R, De Luca M, Travaglino A, et al. Treatments and overall survival in patients with Krukenberg tumor. *Arch Gynecol Obstet.* 2019;300:15-23.
12. Moher D, Shamseer L, Clarke M, et al; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4:1.
13. Whiting PF, Rutjes AW, Westwood ME, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155:529-536.
14. Travaglino A, Raffone A, Saccone G, et al. Immunohistochemical nuclear expression of β-catenin as a surrogate of *CTNNB1* exon 3 mutation in endometrial cancer. *Am J Clin Pathol.* 2019;151:529-538.
15. Travaglino A, Raffone A, Saccone G, et al. PTEN immunohistochemistry in endometrial hyperplasia: which are the optimal criteria for the diagnosis of precancer? *APMIS.* 2019;127:161-169.
16. Raffone A, Travaglino A, Saccone G, et al. PAX2 in endometrial carcinogenesis and in differential diagnosis of endometrial hyperplasia: a systematic review and meta-analysis of diagnostic accuracy. *Acta Obstet Gynecol Scand.* 2019;98:287-299.
17. Travaglino A, Raffone A, Saccone G, et al. Complexity of glandular architecture should be reconsidered in the classification and management of endometrial hyperplasia. *APMIS.* 2019;127:427-434.
18. Lam KY, Lo CY, Kwong DL, et al. Malignant lymphoma of the thyroid: a 30-year clinicopathologic experience and an evaluation of the presence of Epstein-Barr virus. *Am J Clin Pathol.* 1999;112:263-270.
19. Belal AA, Allam A, Kandil A, et al. Primary thyroid lymphoma: a retrospective analysis of prognostic factors and treatment outcome for localized intermediate and high grade lymphoma. *Am J Clin Oncol.* 2001;24:299-305.
20. Thieblemont C, Mayer A, Dumontet C, et al. Primary thyroid lymphoma is a heterogeneous disease. *J Clin Endocrinol Metab.* 2002;87:105-111.
21. Kim HC, Han MH, Kim KH, et al. Primary thyroid lymphoma: CT findings. *Eur J Radiol.* 2003;46:233-239.
22. Lerma E, Arguelles R, Rigla M, et al. Comparative findings of lymphocytic thyroiditis and thyroid lymphoma. *Acta Cytol.* 2003;47:575-580.
23. Gupta N, Nijhawan R, Srinivasan R, et al. Fine needle aspiration cytology of primary thyroid lymphoma: a report of ten cases. *Cytojournal.* 2005;2:21.
24. Cho JH, Park YH, Kim WS, et al. High incidence of mucosa-associated lymphoid tissue in primary thyroid lymphoma: a clinicopathologic study of 18 cases in the Korean population. *Leuk Lymphoma.* 2006;47:2128-2131.
25. Sato Y, Nakamura N, Nakamura S, et al. Deviated VH4 immunoglobulin gene usage is found among thyroid mucosa-associated lymphoid tissue lymphomas, similar to the usage at other sites, but is not found in thyroid diffuse large B-cell lymphomas. *Mod Pathol.* 2006;19:1578-1584.
26. Colović M, Matić S, Kryeziu E, et al. Outcomes of primary thyroid non-Hodgkin's lymphoma: a series of nine consecutive cases. *Med Oncol.* 2007;24:203-208.
27. Niitsu N, Okamoto M, Nakamura N, et al. Clinicopathologic correlations of stage IE/IIE primary thyroid diffuse large B-cell lymphoma. *Ann Oncol.* 2007;18:1203-1208.
28. Moshynska OV, Saxena A. Clonal relationship between Hashimoto thyroiditis and thyroid lymphoma. *J Clin Pathol.* 2008;61:438-444.
29. Avenia N, Ragusa M, Cirocchi R, et al. Surgical treatment of primitive thyroid lymphoma. *Tumori.* 2009;95:712-719.
30. Hwang YC, Kim TY, Kim WB, et al. Clinical characteristics of primary thyroid lymphoma in Koreans. *Endocr J.* 2009;56:399-405.
31. Sun TQ, Zhu XL, Wang ZY, et al. Characteristics and prognosis of primary thyroid non-Hodgkin's lymphoma in Chinese patients. *J Surg Oncol.* 2010;101:545-550.
32. Lee SC, Hong SW, Lee YS, et al. Primary thyroid mucosa-associated lymphoid tissue lymphoma; a clinicopathological study of seven cases. *J Korean Surg Soc.* 2011;81:374-379.
33. Mian M, Gaidano G, Conconi A, et al. High response rate and improvement of long-term survival with combined treatment modalities in patients with poor-risk primary thyroid diffuse large B-cell lymphoma: an International Extranodal Lymphoma Study Group and Intergruppo Italiano Linfomi study. *Leuk Lymphoma.* 2011;52:823-832.
34. Onal C, Li YX, Miller RC, et al. Treatment results and prognostic factors in primary thyroid lymphoma patients: a rare cancer network study. *Ann Oncol.* 2011;22:156-164.
35. Watanabe N, Noh JY, Narimatsu H, et al. Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24553 patients with Hashimoto's disease. *Br J Haematol.* 2011;153:236-243.
36. Alzouebi M, Goepel JR, Horsman JM, et al. Primary thyroid lymphoma: the 40 year experience of a UK lymphoma treatment centre. *Int J Oncol.* 2012;40:2075-2080.
37. Nam M, Shin JH, Han BK, et al. Thyroid lymphoma: correlation of radiologic and pathologic features. *J Ultrasound Med.* 2012;31:589-594.
38. Oh SY, Kim WS, Kim JS, et al. Primary thyroid marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type: clinical manifestation and outcome of a rare disease—Consortium for Improving Survival of Lymphoma Study. *Acta Haematol.* 2012;127:100-104.
39. Cha H, Kim JW, Suh CO, et al. Patterns of care and treatment outcomes for primary thyroid lymphoma: a single institution study. *Radiat Oncol J.* 2013;31:177-184.

DOI: 10.1093/AJCP/AQZ145

40. Ma B, Jia Y, Wang Q, et al. Ultrasound of primary thyroid non-Hodgkin's lymphoma. *Clin Imaging.* 2014;38:621-626.
41. Watanabe N, Narimatsu H, Noh JY, et al. Rituximab-including combined modality treatment for primary thyroid lymphoma: an effective regimen for elderly patients. *Thyroid.* 2014;24:994-999.
42. Chai YJ, Hong JH, Koo do H, et al. Clinicopathological characteristics and treatment outcomes of 38 cases of primary thyroid lymphoma: a multicenter study. *Ann Surg Treat Res.* 2015;89:295-299.
43. Knief J, Gebauer N, Bernard V, et al. Oncogenic mutations and chromosomal aberrations in primary extranodal diffuse large B-cell lymphomas of the thyroid—a study of 21 cases. *J Clin Endocrinol Metab.* 2015;100:754-762.
44. Li XB, Ye ZX. Primary thyroid lymphoma: multi-slice computed tomography findings. *Asian Pac J Cancer Prev.* 2015;16:1135-1138.
45. Wei X, Li Y, Zhang S, et al. Evaluation of primary thyroid lymphoma by ultrasonography combined with contrast-enhanced ultrasonography: a pilot study. *Indian J Cancer.* 2015;52:546-550.
46. Yang L, Wang A, Zhang Y, et al. 12 Cases of primary thyroid lymphoma in China. *J Endocrinol Invest.* 2015;38:739-744.
47. Gu LS, Cui NY, Wang Y, et al. Comparison of sonographic characteristics of primary thyroid lymphoma and anaplastic thyroid carcinoma. *J Thorac Dis.* 2017;9:4774-4784.
48. Li P, Zhang H. Ultrasonography in the diagnosis and monitoring of therapy for primary thyroid lymphoma [published online December 28, 2018]. *Ultrasound Q.*
49. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. *Autoimmun Rev.* 2014;13:391-397.
50. Stone MD, Wallace RB. *Medicare Coverage of Routine Screening for Thyroid Dysfunction.* Washington, DC: National Academies Press; 2003.
51. Yoo J, Ahn HS, Kim SJ, et al. Evaluation of diagnostic performance of screening thyroid ultrasonography and imaging findings of screening-detected thyroid cancer. *Cancer Res Treat.* 2018;50:11-18.
52. Teixeira Mendes LS, Wotherspoon A. Marginal zone lymphoma: associated autoimmunity and auto-immune disorders. *Best Pract Res Clin Haematol.* 2017;30:65-76.
53. Peng H, Du M, Diss TC, et al. Genetic evidence for a clonal link between low and high-grade components in gastric MALT B-cell lymphoma. *Histopathology.* 1997;30:425-429.
54. Chan JK, Ng CS, Isaacson PG. Relationship between high-grade lymphoma and low-grade B-cell mucosa-associated lymphoid tissue lymphoma (MALToma) of the stomach. *Am J Pathol.* 1990;136:1153-1164.
55. Zelenetz AD, Gordon LI, Abramson JS, et al. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas*. Version 3.2019. 2019. Available at https://www.nccn.org/professionals/physician_gls/default.aspx#site.

DOI: 10.1093/AJCP/AQZ145