Peer Review File

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Reviewer A

The authors reported the characteristics of 22 patients with PTL who were diagnosed using immunoglobulin clonal gene arrangements and immunostaining of the tissues. PTL is a rare disease, hence making diagnoses and treating patients are difficult in some ways.

Specific Comments:
Comment 1: This article contains the information which have been already known and used in clinical practice.
Reply 1: We appreciate this good suggestion very much. This article was an observational article, describing diagnoses modalities, treatments and survival situations of PTL patients. Clinical doctor knows little about the features and treatment strategy of PTL due to its rareness. There were a few sporadic reports of PTL, and the largest number of literatures had only included 119 cases, even fewer reported in China. Considering this situation, we collected more than 20 patients to provide our experience. We wish to include more cases to and contribute to the standard therapy of PTL.

Comment 2: The study includes 4 patients with the stage higher than 3E, though in the texts, they excluded those patients.
Reply 2: We are sorry for bringing ambiguity to the editorial department. PTL was defined as primary thyroid lymphoma with or without involvement of the local lymph nodes in the neck, and any other involvement beyond these limits occurred at the time of the first diagnosis was excluded. Patients with the stage higher than 3E were diagnosed stage I/II at first diagnosis, and then were revealed beyond neck during follow-up period.
Changes in the text: we have modified our text as advised **(see Page 6, Line143-144:**Patients with the stage III/IV were diagnosed stage I/II at first diagnosis, and then were revealed beyond neck during follow-up period.)

Comment 3: Diagnosis of HT should be based on pathological results, since all the patients underwent biopsy, or at least FNA.
Reply 3: Thank you very much for the valuable suggestions, and sorry for no clarity of defining HT. According to reference: Travaglino A PM, Varricchio S, et al. Hashimoto Thyroiditis in Primary Thyroid Non-Hodgkin Lymphoma. Am J Clin Pathol. 2020;153(2):156-64. “The diagnosis of HT is based on clinical features, serum antithyroid antibodies, sonographic features, and pathologic examination. “Among 22 patients, the pathological results of 15 patients indicated HT background. Whereas, pathological results of no.14 patient shows node full of lymphoma tissue without normal thyroid tissue, so we defined this patient as HT based on positive antithyroid antibodies and enlarged thyroid tissue.
Changes in the text: we have modified our text as advised (**see Page 4, line 81:**HT was diagnosed as presence of pathological evidence combined with antithyroid antibodies and clinical history of HT.)

Comment 4: If possible, the protocol of deciding treatments (surgery, RT or CMT) should be mentioned.
Reply 4: We appreciate it very much for this good suggestion. Because thyroid lymphoma is difficult to diagnose by FNA, especially interfered with Hashimoto's thyroiditis. PTL is generally pathologically confirmed after surgical resection. Stage IE MALT patients accept surgery or RT only, while DLBCL or MALT beyond thyroid chose surgery plus chemotherapy or CMT treatment.

Changes in the text: we have modified our text as advised (**see Page 4, line 87-88 :** Stage IE MALT undertook surgery or radiotherapy only, while beyond thyroid or other types chose chemotherapy following surgery or CMT treatment.)

Comment 5: No explanation was given in the article about double-hit, or triple-hit lymphoma. It should be given.
Reply 5: We appreciate it very much for this helpful advice. Double-hit lymphoma (DHL) is recognized as "high grade B-cell lymphoma (HGBL) with rearrangements of MYC and BCL2 or BCL6". Triple-hit lymphoma (THL) is defined as B-cell lymphoma with chromosomal alterations in MYC, BCL2, and BCL6 and has a similar prognosis to DHL. (Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.) Diffuse large B-cell lymphomas with aberrations in MYC, BCL2 and/or BCL6 by genetic alterations or protein expression represent a group of high grade B-cell lymphomas with worse outcomes when treated with standard RCHOP chemotherapy.(Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. Blood Rev. 2017 Mar;31(2):37-42.)
Changes in the text: We have modified our text as advised **(see Page 4-5, line 98-101** : Double-hit lymphoma (DHL) is recognized as "high grade B-cell lymphoma (HGBL) with rearrangements of MYC and BCL2 or BCL6" . Triple-hit lymphoma (THL) is defined as B-cell lymphoma with chromosomal alterations in MYC, BCL2, and BCL6 and has a similar prognosis to DHL)

Reviewer B

The title needs to be amended

The manuscript needs significant grammatical and punctuation correction, I suggest using any of the grammatical services for correction

Some sentences need to be well formulated scientifically

Some sentences are unclear, need more clarification

The Role of HBV testing is not clear as part of the design of the study or was just an observation during the study

The methods section needs to be more summarized without affecting the general meaning

The first paragraph in discussion should be included as part of the conclusion

The conclusion section should be more summarized and just including few sentences

Some of the references are very old, needs more recent references

Specific Comments:

Comment 1: The title needs to be amended

The manuscript needs significant grammatical and punctuation correction, I suggest using any of the grammatical services for correction

Some sentences need to be well formulated scientifically

Some sentences are unclear, need more clarification

Reply 1: We are sorry for the editorial department caused by the grammar problems in this article. Since we are not native language speaker, we would like to accept the extensive language editing:the Article Processing Charge editing services.
Changes in the text:we have modified our title: Clinicopathological analysis of primary thyroid non-Hodgkin' s lymphoma: a single center study, and our text as advised **(see Line 33-34,45,48,51,60, 61,62, 63, 68, 70,85,88,104,107- 109,109-110, 141,151)**

Comment 2: The Role of HBV testing is not clear as part of the design of the study or was just an observation during the study

Reply 2: Thank you for your comments. It is reported that hepatitis B virus influence the function of B cells, and HBV infection response poor to chemotherapy than those without HBV. (Wang Y WH, Pan S, et al. Capable Infection of Hepatitis B Virus in Diffuse Large B-cell Lymphoma. J Cancer. 2018;9(9):1575-81;Lemaitre M BP, Frigeni M, et al. Hepatitis B virus-associated B-cell non-Hodgkin lymphoma in non-endemic areas in Western Europe: Clinical characteristics and prognosis. J Infect. 2020;80(2):219-24.) We wanted to compare the survival situations between patients with or without HBV in our study. However, there is no significant difference between two groups.

Comment 3: The methods section needs to be more summarized without affecting the general meaning

Reply 3: We appreciate it very much for this good suggestion, and we refined and reorganized the methods section.

Changes in the text: we have modified our text as advised (**see Page 4, line 79 :** HT was diagnosed as presence of pathological evidence combined with antithyroid antibodies and clinical history of HT**. 87-88:** Stage IE MALT undertook surgery or radiotherapy only, while beyond thyroid or other types chose chemotherapy following surgery or CMT treatment、**98-101 :** Double-hit lymphoma (DHL) is recognized as "high grade B-cell lymphoma (HGBL) with rearrangements of MYC and BCL2 or BCL6" . Triple-hit lymphoma (THL) is defined as B-cell lymphoma with chromosomal alterations in MYC, BCL2, and BCL6 and has a similar prognosis to DHL**. Page 5, 108-110:** For the determination of monoclonality, sterile water was included as the negative sample, and target gene sequence plasmid DNA mixture (RIGEN-BIO, Shanghai, CN) as the positive sample**.**)

Comment 4: The first paragraph in discussion should be included as part of the conclusion

Reply 4: We appreciate it very much for this helpful suggestion. In the first paragraph of discussion part, we add the purpose, methods and results of our study briefly.

Changes in the text: We have modified our text as advised (**see Page 7, line 167-174** : We undertook a retrospective study to describe the clinical characters, pathological features, survival situations and immunoglobulin clonal gene rearrangements of PTLs in our medical center. As a result, PTL affects middle aged and old female with HT, and its main histological type is non-Hodgkin' s B cell lymphoma, mostly DLBCL, following with MALT, which accordance with previous literature. Prognosis depend much on subtypes and stages, so early diagnose is important. For patients with HT along with histologically benign lymphoepithelial lesion, which is suspicious for PTL, Ig clonal gene rearrangements is essential for differential diagnosis. Disease free survival and overall survival between DLBCL and MALT was not statistically significant in our research.)

Comment 5: The conclusion section should be more summarized and just including few sentences

Reply 5: We appreciate it very much for this good advice, and we have taken reviewers advice to refine the conclusion part.

Changes in the text: We have modified our text as advised (**see Page 11-12, line 283-290** : PTL affects female patients in their 5th and 6th decades, and its main histological type is non-Hodgkin' s B cell lymphoma. Suspicious lump should take FNA biopsy, and be differentiated from thyroiditis and thyroid solid tumor by means of flow cytometry or immunohistochemical staining. For patients with HT along with histologically benign lymphoepithelial lesion, identification of Ig clonal gene rearrangements is important for routine differential diagnosis. There is no significant difference of prognosis between DLBCL and MALT in our study, probably due to the small sample. Further research of new diagnostic markers and therapeutic

targets at the molecular level for effective management is needed.)

Comment 6: Some of the references are very old, needs more recent references
Reply 6: We appreciate it very much for this helpful advice, and we update references in our manuscript.
Changes in the text: We have modified our references as advised. We transfer **"Holm LE BH, Löwhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med. 1985;312(10):601-4.**"to "**Hirokawa M, Suzuki A, Hashimoto Y, Satoh S, Canberk S, Jhuang JY, et al. Prevalence and diagnostic challenges of thyroid lymphoma: a multi-institutional study in non-Western countries. Endocr J. 2020;67(11):1085-91.** "; "**Takashima S NN, Noguchi Y, Matsuzuka F, Inoue T. Primary thyroid lymphoma: evaluation with US, CT, and MRI. J Comput Assist Tomogr. 1995;19(2):282-8**."to"**Aiken AH. Imaging of thyroid cancer. Semin Ultrasound CT MR. 2012;33(2):138-49**."
