Peer Review File

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Reviewer A

Comment: Thorough clinical description of what is a rare entity in western countries. The major drawbacks are the retrospective single centre nature of the publication. Molecular correlations would also be very useful insights into the diagnosis and potential management of these patients.

Reply: We thank the reviewers for their valuable suggestions. Although skin is the most common site of extranodal organ involvement in patients with Extranodal natural killer/T-cell lymphoma (ENKTL), cutaneous ENKTL is still rare. It's a pity that the study was carried out in a single center. In fact, we are planning to verify it in further larger multicenter collaborative groups. We also hope to conduct further studies to explore specific molecules or markers related to the pathogenesis and prognosis of cutaneous ENKTL.

Reviewer B

Comment 1: The introduction is too short. This part should be written to explain the current status of the cutaneous ENKTL (for example, any other large series of ENKTL before? If yes, what is not yet known based on that study; If no, this would be the niche for this study to add to the current knowledge of ENKTL.

Reply 1: Thank you very much for the suggestion. Cutaneous ENKTL has a short survival time and shows poor response to therapy; one study reported a median progression-free survival of 12 months and 2-year overall survival (OS) of 29.0 months, with an OS rate of 48% and 12-month survival rate of 40% for advanced-stage disease. Secondary cutaneous ENKTL has a more aggressive clinical course and worse outcome than primary cutaneous ENKTL. However, these findings

are based on a small number of studies and case reports, and the detailed clinical features and prognosis of cutaneous ENKTL have not been fully elucidated.

Changes in the text: See Page 2, line 46-48; Page 3, line 49-52.

Comment 2: Figure 3, survival curve (overall survival), "censored" and "noncensored" are used in the figure annotation but not in the figure curve itself. Please explain.

Reply 2: We double checked the figure, and found out that "censored" and "noncensored" are used in the both figure annotation and the figure curve itself. It may be that the number of censored cases is so small that it is not obvious.

Comment 3: Figure 2, please add clinical pictures of specific types (as listed in the Table 1, say, nodules, ulcerations, erythema, ringworm-like lesions, and swelling).

Reply 3: Considering reviewer's suggestion, we re-selected photos with typical clinical manifestations, including ringworm-like lesions, nodules, ulcerations, erythema, and confluent lesion.

Changes in the text: See Figure 2.

Comment 4: Table 2, the abbreviations should be listed alphabetically.

Reply 4: The list of abbreviations was rearranged alphabetically to make it easier to read. In addition, in order to increase the rigorism of the table, the details were revised again, such as add footnote symbols for annotation and corrected capitalization of letters.

Changes in the text: See Table 2.

Comment 5: Table 3, abbreviation list should be made. For example, EBER, an CD3e.

Reply 5: We have added abbreviation as suggested of Table 3.

Changes in the text: See Table 3.

Comment 6: Table 4, the statistical analysis should be explained further. For example, for multivariate analysis, what covariates have been chosen and what about the HR for these "presumably non-significant" covariates? What are the associations between hemogram and IPI?

Reply 6: We put the statistically significant parameters (B symptoms, stage, LDH, hemoglobin, IPI) of univariate analysis into multivariate analysis. HR, 95%CI and *P* values of multivariate analysis covariates are added in the text. At present, we can't explain the relationship between hemoglobin and IPI. Maybe further research could establish a specific prognosis model for cutaneous ENKTL.

Changes in the text: See Page 8, line 176-178, line 180-182.

Reviewer C

Major revisions:

Comment 1: Firstly, a major issue that needs to be clarified is the different treatment options established for the disease control. Since there was no consensus on the treatment choice and due to the heterogeneity of the cases (primary skin involvement vs secondary skin involvement), I would suggest that the authors clearly separate the treatment options according to the stage and disease subtype. Recent studies highlight the unique efficacy of L-asparginase in late disease stages. Furthermore, anthracycline – based chemo, such as CHOP is known to be not useful; how do the investigators explain the CHOP initiation in two patients?

Reply 1: Previous reports have shown that traditional anthracycline-based chemotherapies, even when combined with RT, is not effective. Since 2001, Kim WS, et. al. had (Ann. Oncol, 2001 Mar;12(3):349-52) reported that four cycles of CHOP followed by involved field radiation therapy was not satisfactory for treating patients with localized nasal NK/T-cell lymphoma. Patients with cutaneous ENKTL from November 2000 to July 2016 were included in our study. In fact, all patients with ENKTL in our institute have been using the asparaginase-based regimen since 2008. Before the pegaspargase was put on the market, asparaginase-based regimen was replaced by a CHOP regimen if the skin test was positive.

Comment 2: Although it seems that there was no consensus on treatment choice among the investigators, it would be interesting to have more details on how the different treatments were chosen (e.g. according to performance status, advanced stage, LDH or nasal vs non- nasal type disease etc).

Reply 2: Firstly, according to stage and international prognostic index (IPI) score, early stage or low risk patients usually choose VDLP (vincristine, daunorubicin, L-asparaginase, and prednisone)、LVP (L-asp, vincristine, and prednisolone). Advanced stage or moderate to high risk patients need stronger chemotherapy plan, SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) can be considered. Secondly, it is necessary to assess whether the patient's performance status can withstand the chemotherapy plan. Finally, the patient's underlying disease needs to be evaluated. For example, platinum containing solutions should be avoided when patients have a potentially damaging kidney or has one kidney or hyfronephrosis.

Changes in the text: See Page 6, line 141-143.

Comment 3: In addition, the role of radiotherapy should be more specified. In a recent study by CP Fox et al. (Lancet, 2020) the authors present persuasive data that radiation is an important component of therapy, especially during the early disease stages.

Reply 3: We have corrected as suggested. In the results section, we gave a more detailed description of the patients receiving chemotherapy or radiochemotherapy. The treatment effect was compared between the treatment groups，complete remission (CR) was achieved in 2 (14%) of 14 patients receiving only chemotherapy, 3 (50%) of 6 patients receiving chemotherapy plus radiotherapy. We analyzed the result in the discussion section, and specified the role of radiotherapy in ENKTL and cutaneous ENKTL. Many researches have shown a role of radiotherapy in treating localized disease. However, the value of radiotherapy in advanced patients needs to be further studied and validated.

Changes in the text: See Page 7, line 151-152; Page 10, line 237-240； Page 11, line 241-242.

Comment 4: The authors explain very well that dismal disease characteristics (such as B – symptoms, advanced staging and high LDH) were linked to a poor prognosis. However, what is missing and may be clinically relevant especially for the decision-making is the performance (ECOG) status. Therefore, I think that it would be interesting to include the ECOG status to this analysis (if available from patients` records)

Reply 4: We thank the reviewer's valuable suggestion. It is true that ECOG should be included in the survival analysis, but in this retrospective analysis, the history of ECOG has some deficiencies in the record, while the record of IPI score is relatively complete. We will further improve the data recording in the future clinical work. In fact, IPI scores which include age, stage, ECOG, Extranodal lesion and LDH, can better reflect the prognosis to a certain extent.

Comment 5: The discussion section is rather long. It should be more compact and include only the important conclusions deriving from the current study. According to my opinion, authors should concentrate on treatment and clinicopathological characteristics, as mentioned in the title of the manuscript. In some points, the discussion section does not summarize an important finding from the study but rather reviews and postulations from existing literature.

Reply 5: We have modified our text as advised. The clinical features, pathological findings and treatment were also discussed. Some unnecessary discussion (e.g. how to stage in patients with combined lesions) were avoided. Pathological findings emphasized higher expression of surface CD3, and the reasons are analyzed. It is tempting to hypothesize that the different expression of CD3 in nasal and cutaneous ENKTL reflects a difference in tumor origin or pathogenesis, ENKTL with cutaneous involvement maybe different subgroups. In addition, we discussed CD56 negative expression in ENKTL, talked about previous studies observed that patients with

extranasal upper aerodigestive tract involved were more likely to have CD56 negative, 20% of true NK-cell tumors with germline T-cell receptor-γ gene and 45% of the T-cell-derived tumors lacked CD56 expression. CD56-negative patients require a combination of cytotoxic markers and EBER analysis to diagnose ENKTL. To discuss the treatment results, the radiotherapy part was rewritten to clarify the role of radiotherapy in ENKTL and cutaneous ENKTL. Many researches have shown a role of radiotherapy in the treatment of localized disease. However, the value of radiotherapy in advanced patients needs further studied and validated.

Changes in the text: See Page 8, line 186-191; Page 9, line 210-216; Page 10, line 237-242.

Minor revisions:

Comment 1: In order to better assess the treatment outcome, I would suggest to also refer to the median follow – up time of the patients.

Reply 1: We have modified our text as advised. The median duration of follow-up was 4.0 months (range 1.0–32.0 months).

Changes in the text: See Page 7, line 153-154.

Comment 2: Abstract section and Result section (p. Treatment and evaluation): "The presence of B symptoms, stages, increased level …": I think you mean "advanced stage" instead of "stages". I so, please correct accordingly.

Reply 2: We have modified our text as advised.

Changes in the text: See Page 1, line 16; Page 8, line 174.