

Peer Review File

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Reviewer A

The tracheal fistula is not rare after treatment, especially when its effect is excellent. Please collect the cases of outstanding effect of treatment (i.e. EBRT or other chemotherapy). There is little scientific contribution from this manuscript.

Reply: I'm glad that you have reviewed this article. We will collect these cases according to your opinions. thank you.

Reviewer B

Comment 1: Some abbreviations should be specified, e.g. CVP in the abstract, ECT on page 2, CNB page 3.

Reply 1: agreed. We changed the abbreviations. The abbreviation of ECT has been changed and I have added a list of abbreviations.

Changes in the text: we have modified our text as advised (see Page 3 line 7, Page 3 line 10,16,19)

Comment 2: For biological measurements, normal values should be provided.

Reply 2: agreed. We provide specific measurement sizes.

Changes in the text: we have modified our text as advised (see Page 2, line 22; Page 3, line 2)

Comment 3: I think that the last sentence of the case presentation should be modified with suppression of “it’s a pity that family gave up treatment”

Reply 3: Agreed. Has been replaced with “it’s a pity that family gave up treatment”

Changes in the text: we have modified our text as advised (see Page 5, line 11)

Comment 4: the clinical case could be more synthetic, some parts can be deleted

and others more detailed. For example, the part related to physical examination with speculations of thyroid volume estimation is not necessary. In contrast, the neck US report should specify the presence of lymph-nodes which are described on PET/CT. Apparently a scintiscan was performed. It needs to be said more clearly.

Reply 3: Agreed. According to your suggestion, we have deleted part of the contents of the physical examination. Although lymph nodes were reported by PET-CT, neck ultrasound did not describe lymph nodes, possibly due to sensitivity.

Changes in the text: we have modified our text as advised (see Page 3, line 4)

Comment 4: It is important to stress the difficulty of diagnosing thyroid lymphoma because very rare cases of Riedel's thyroiditis can be hard to differentiate. Anaplastic thyroid cancer is another differential diagnosis.

Reply 4: Agreed. We added this part.

Changes in the text: we have modified our text as advised (see Page 5, line 17)

Comment 5: The pretherapeutic evaluation of thyroid lymphoma should also be specified. The authors provide the report of PETC/CT showing major extrathyroidal extension and possibly lymph-node involvement, but no distant sites. A dedicated PET figure should be useful. If extrathyroidal extension was important why bronchoscopy and esophagoscopy were not performed before chemotherapy? They might have been able to highlight a tracheal or esophageal invasion and contraindicate chemotherapy.

Reply 5: Agreed. But we haven't seen cases of tracheoesophageal fistula caused by chemotherapy. We usually use neck CT to evaluate the trachea of patients, so we didn't do tracheoscopy before treatment. we added pictures of the esophagus before treatment.

Changes in the text: we added some data. (see Page 3, line 14)

Comment 6: The mechanism of fistula after chemotherapy is not well understood. It could be interesting to discuss the similar known side effects of tyrosine kinase

inhibitors such as Lenvatinib in locally advanced thyroid cancer (Blevins et al, Thyroid 2014; 24(5): 918–922).

Reply 6: Agreed. It is interesting and we have added this part.

Changes in the text: we added some data. (see Page 7, line 11)

Reviewer C

Comment 1: In addition to tracheostomy and tracheal stenting to secure the airway, radiotherapy may have been used to avoid rapid tumor shrinkage due to chemotherapy. Please describe carefully treatment options based on the risks, benefits, and outcomes of tracheostomy, surgical decompression, tracheal metal stents, external irradiation, and high-dose corticosteroids.

Reply 1: Agreed. In addition to tracheostomy and Tracheal stenting, Radiotherapy is also a treatment. Due to the low incidence, the current treatment is controversial.

The role of surgical intervention in the treatment of PTL is still controversial. Studies have confirmed that surgery for thyroid lymphoma (stage IE) is the main treatment method and no adjuvant treatment is required after surgery. Studies have also shown that because radiotherapy and chemotherapy can aggravate the obstruction caused by tissue swelling, it is still considered that palliative surgery can relieve severe airway obstruction before radiotherapy and chemotherapy.

At present, there are still some shortcomings in airway stent implantation, including stent obstruction and difficult removal.

Combination therapy has certain advantages. Combination chemotherapy reduces the incidence of distant recurrence, and local radiotherapy reduces the risk of low local recurrence.

Comment 2: RCHOP therapy is also commonly used for DLBCL, why did you choose CVP therapy?

Reply 2: The standard chemotherapy for DLBCL is R-CHOP. There are few studies on rituximab in the treatment of PTL. When R-CHOP was used in the past, one patient had obvious adverse reactions and emotional excitement. Combined with previous

experience, CVP chemotherapy also has good effect.

Reviewer D

Comment 1: Background, page 2, Line, 35-36. There are several articles reporting invasive PTL. Though it is rare, PTL seems to have invasive ability potentially. You cannot really say that PTL does not invade the trachea.

Reply 1: Agreed. I've changed it

Changes in the text: we have modified our text as advised (see Page 2, line 15)

Comment 2: The figure of CT suggested perforation of the trachea or esophagus, but it is not enough convincing to prove the existence of tracheoesophageal fistula to the readers. Figures of fistulography or both bronchoscopy and endoscopy will help them satisfied. If there is a limit to the number of figures, the figure of pathology is unnecessary.

Reply 2: Agreed. I have added pictures of the patient's fiberoptic bronchoscopy, and deleted some pathological pictures

Changes in the text: we have modified our text as advised (see Page 4, line 4,21)

Comment 3: It would be better to add the IL-2 receptor level before treatment in the Case presentation section.

Reply 3: We are very sorry, I checked the data, we detected IL-6 level, but did not detect IL-2 receptor level.

Comment 4: Discussion, page 5, Line 126. "his patient"; this is a typographical error.

Reply 3: Agreed. I have corrected this mistake.

Changes in the text: we have modified our text as advised (see Page 6, line 22)

Comment 5: The title is “Tracheoesophageal fistula 1 caused by chemotherapy in primary thyroid lymphoma”. So, the Discussion section should be focused on the invasive ability of PTL and strategy for prevention and treatment of fistula. This manuscript is not sufficient to explain these contents. The authors cited only one article (Chen C, 2013), but it would be useful to include other articles such as below. Kongpolprom, Napplika. "Tracheal Perforation following Chemotherapy of Diffuse Large B-Cell Lymphoma." Case Reports in Acute Medicine 1.1 (2018): 1-6.

Jaremko, J. L., B. Rawat, and S. Naik. "Oesophageal and tracheal perforation in thyroid B-cell lymphoma." Australasian radiology 51 (2007): B193-B195.

Tachibana, Tomoyasu, et al. "Diffuse large B-cell lymphoma of the thyroid which caused esophageal fistula." Esophagus 12.1 (2015): 77-81.

Anagnostis, Panagiotis, et al. "Esophageal perforation in case of thyroid lymphoma." Clinical Case Reports 8.7 (2020): 1313-1314.

Reply 5: Thank you very much for your advice. I have added these contents. And we quoted some references.

Changes in the text: we added some data (see Page 2, line 16)

Comment 6: If there is a limit to the number of words, the discussion of pathological diagnosis (such as FNA and CNB) is unnecessary.

Reply 6: Agreed. I revised this part and simplified it.

Comment 7: Reference. No. 6, 14, and 15 are the same references.

Reply 7: Learning from your rigorous attitude, I revised the references again.

Changes in the text: we have modified our text as advised (see Page 9, line 2)