

Peer Review File

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Reviewer A

The authors presented here a case of multiple ciliated muconodular papillary tumor in a 55 yo smoking man. Squamous cell metaplasia with budding was noted in 1 nodule. Response: Thank you for your summary of the content of the article, we are submitting a revised manuscript. Detailed point-by-point responses to these questions are provided below.

Comment 1: I would suggest to add a column with molecular features of previous cases of CMPT and the present one in Table 1.

Reply 1: Thanks for your suggestion, we have added molecular features as advised in Table 1 (see Page 19-20, second column on the right).

Changes in the text: “molecular features...”

Comment 2: Data on results of frozen section in the current and previous cases could be interesting for readers. Please add this in another column.

Reply 2: Thank you for your valuable suggestions on how to increase readers' interest in this article. However, we did not clearly understand the data you said about frozen sections, because we listed all the intraoperative frozen results mentioned in the cited articles in the last column of Table 1. In addition, because the information listed in the Table 1 is already very large, in order to make the table concise, it is difficult to expand the information of frozen results or add an additional column of data. Of course, we look forward to your response to our concerns, and are willing to continue to improve the article under your guidance.

Changes in the text: None.

Comment 3: Details on NGS platform and panels are required in M&M section.

Reply 3: We have taken note of this detail and thank you for your suggestion. Unfortunately, we are unable to provide detailed information about NGS, as the patient's NGS was done during a consultation in the pathology department of Zhongshan Hospital Affiliated to Fudan University (one of the leading hospitals in China), and we only obtained the final NGS test results of the patient. We also tried to communicate with the pathology department of the hospital, but they were not willing to disclose the test method.

Changes in the text: None.

Comment 4: May the authors robustly state here that nodules in the right lung are radiologically consistent with ciliated muconodular papillary tumor? Please state.

Reply 4: Thanks for your concerns, we have revised the content of the article and explained that some of the right pulmonary nodules and left pulmonary CMPT showed

consistency on imaging findings. We have modified our text as advised (see Page 6, line 169-173).

Changes in the text: “In our case, some nodules in the right lung showed radiographic features consistent with BAs in the left lung, such as irregular borders, small cavities and solid components, especially the nodule in Figure 2C. Combined with the tumor growth characteristics, we suspect that multiple nodules in the right lung are also BAs, which may be the first case of multiple BAs in both lungs.”

Reviewer B

Thank you for this interesting case report on this rare lung premalignant condition:

I have some questions/comments:

Response: Thank you for your interest in the content of the article, we are submitting a revised manuscript. Detailed point-by-point responses to these questions are provided below.

Comment 1: Please clarify if wedge or segmentectomy was performed, it seemed wedge was used and sometimes segment was used.

Reply 1: Thanks for your careful observation, we have made a supplement to the missing point. We use both methods, since 4 nodules were in close proximity, segmentectomy of S9+10 was performed, and the other was performed by wedge resection. We have revised our article to address your concerns (see Page 4, line 100 and Page 8-9, line 251-253)

Changes in the text: “...segmentectomy” and “The number and location of the nodules also affect the choice of surgical procedure, which is why we performed S9+10 segmentectomy...”

Comment 2: do you think wedge is adequate and one lesion is adequate for diagnosis once you know it is BA, then you can stop?

Reply 2: Thank you for your question. None of the current reports suggest recurrence or metastasis of BA. Therefore, we believe that wedge resection is adequate for a definite diagnosis of BA. However, due to the gradual discovery of the biological characteristics of BA, postoperative imaging follow-up is still necessary.

Changes in the text: None.

Comment 3: Do the authors recommend resecting all lesions?

Reply 3: For pulmonary nodules with high suspicion of malignancy, complete removal is recommended. However, it depends on a number of factors, such as the location of the nodule, the extent of the nodule to be removed, the patient's lung function, and so on. For our patient, considering multiple nodules in the right lung as BAs, we chose postoperative follow-up. If the nodules are radiographically progressive, we recommend surgery and remove as much of the lesion as possible to eliminate the risk.

Changes in the text: None.

Comment 4: What is the recommended f/u time for these lesions s/p resection? 5 years? indefinitely?

Reply 4: Your question is also what we are facing. At present, there is no uniform recommended duration of postoperative follow-up. We believe that a full 5-year follow-up is sufficient for patients with complete resection. For our patient, continuous follow-up is necessary because we are not sure that the right lung nodule is also BAs and the possibility of its progression cannot be ruled out. We supplement the content of postoperative follow-up time in this paper (see Page 9, line 260-261).

Changes in the text: “There is currently no recommended duration of follow-up, but 5 years appears to be safe enough for patients with complete resection.”

Reviewer C

This is great case with lot of potential given the multifocality of tumor along with atypical squamous metaplasia and potentially squamous cell carcinoma but is missing some key aspects.

Response: We appreciate the reviewer’s encouragement and helpful comment. We are submitting a revised manuscript. Detailed point-by-point responses to these questions are provided below.

Comment 1: More convincing pictures are required of the squamous atypia and carcinoma.

Reply 1: Thanks for your suggestions, we have added pictures about squamous metaplasia and squamous atypia. But we don't have evidence that it develops into carcinoma. We have add our pictures and modified our text as advised (see Figure 3E and Figure 4C, Page 5, line 121-128).

Changes in the text: “Figure 3 and Figure 4” and “Continuation and transition between squamous metaplasia and ciliated columnar epithelium (Figure 3E).....Atypia appeared in normal squamous metaplastic cells (Figure 4C). ”

Comment 2: A TP53 immunostain and Ki67 may provide added evidence atypia of the squamous metaplasia/carcinoma.

Reply 2: We have added P53 immunohistochemistry, which is not significant enough to support the diagnosis of squamous cell carcinoma. Ki67 was not included in the original pathology, and the supplementary pathological experiment involved the patient's willingness, so we are sorry that we cannot add. We supplemented Figure 4C to confirm atypia of the squamous metaplasia. We have add our pictures and modified our text as advised (see Figure 3I and Figure 4C, Page 4-5, line 123-124).

Changes in the text: “Figure 3 and Figure 4” and “...but basal cells were positive for p53 with varying degrees of intensity (Figure 3I)Atypia appeared in normal squamous metaplastic cells (Figure 4C). ”

Comment 3: Was TP53 gene part of the sequencing panel?

Reply 3: No, it wasn't.

Changes in the text: None.

Comment 4: The focus should be on transformation of squamous metaplasia to SqCC which is the pathway here rather than the malignant potential of BA in itself. BA's malignant transformation is still controversial and mostly into adenocarcinomas. But SqCC arising out of squamous metaplasia is reported in several locations and that should be the focus of this report. The case is novel and will add excellent value but needs to be rewritten in certain aspects. The focus should be on squamous metaplasia to SqCC pathway rather than suggesting BA to be a precursor for SqCC

Reply 4: Thank you for your positive feedback. However, the information we have obtained is not enough to prove that BA can develop into squamous cell carcinoma, and the current results can only suggest that BA has malignant potential. As clinicians, we tend to pay more attention to the benign and malignant of BA. We strongly agree with you that attention should be paid to the pathway of squamous metaplasia to squamous cell carcinoma, but we think this is more appropriate to be written as a review. We are looking forward to your reply and continue to improve the article.

Changes in the text: None.