Peer Review File

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Review Comments-Reviewer A

The authors present three cases of multiple lung adenocarcinomas showing that the molecular analyses help for the diagnosis between synchronous adenocarcinomas and IPM. This manuscript has several major issues.

1) It reports three cases without any new information, as compared to several series published on that subject in the last few years.

Reply: Thank you for your precious comment and advice. In this paper, MPLC and IPM were differentiated by analyzing the pathogenic mutations in the same signaling pathway. Previous studies mainly focused on the driver gene level, and specific analysis on differential diagnosis through the same signaling pathway was rarely conducted. In addition, the sequencing panel used in this test covered 1238 genes related to tumor occurrence and development, making it the test project with the largest number of genes except WES so far.

2) There are issues with two of the cases: The case #1 described different patterns in the text (acinar versus Acinar + papillary) while the figure shows two areas with papillary features. The case #2 shows two minimally invasive adenocarcinomas that are by definition two synchronous tumors and do not merit molecular analysis.

Reply: Thank you for your precious comment and advice.

(1) We have modified the figure of case 1, see the figure 1 revised.

(2) In case 2, Different pathogenic mutations were found in the upstream and downstream of the same signaling pathway. Through molecular detection, the case confirmed multiple primary mutations, which distinguished the nodule types of patients, and it has certain guiding significance for the follow-up treatment of patients. And it has previously been reported that this condition may be intrapulmonary metastasi due to STAS.

3) The discussion is weak and does not underline the novelty of these case reports.

Reply: Thank you for your precious comment and advice, we have enriched the discussion section, see lines163-171.

4) Several recent publications are not referenced (for example: PMID: 35740676, PMID: 34773797, PMID: 33116891, PMID: 36579550, PMID: 36788096)

Reply: Thank you for your precious comment and advice, the references have been added, see lines 297-306.

Review Comments-Reviewer B

line 66: I would use similar instead of identical (identical is too strong wording)
Reply: Thank you for your precious comment and advice, we have modified it.

line 125/126: I would rephrase: She then received right bilobectomy (middle and lower lobe).
Reply: Thank you for your precious comment and advice, we have modified it.

It would be interesting to know which genes are included in the NGS panel (perhaps as supplementary table)
Reply: Thank you for your precious comment and advice, we have added the panel list as supplementary table.

Is it possible to provide additional information about systemic therapy/ radiotherapy these patients received or not?
Reply: Thank you for your precious comment and advice, the information of systemic therapy/radiotherapy for these patients, we're still tracking it, and we'll add to it when we publish it in the future.

Is it possible to include more detailed clinico-pathological information (stage, gender, smoking status etc.) in a summary table?
Reply: Thank you for your precious comment and advice, the clinico-pathological information is shown in the table1.

The lepidic growth pattern is often considered to be in situ growth. The two patients with lepidic component were classified as (MPLC) which seems to be intuitively correct as this would mean that two independent nodules grew synchronously. Please include in the discussion a short paragraph about the prevalence of different growth patterns in cases with MPLC or IPM/satellite nodules. Are there any reports about the association of certain growth patterns with MPLC or IPM/satellite?
Reply: Thank you for your precious comment and advice, we have added the consent about the difference of MPLC and IPM.

Please indicate EGFR and TET2 truncal mutations in Fig. 1C
Reply: Thank you for your precious comment and advice, we have modified the Fig 1C.

Review Comments-reviewer C

The ability to distinguish satellite nodules, multiple primary lung cancers (MPLCs), and intrapulmonary metastases (IPM) is crucial for prognosis and treatment. The traditional diagnostic criteria for MPLC/IPM including the Martini and Melamed (MM) criteria and the comprehensive histologic assessment (CHA) criteria, mainly relies on histological comparison between multiple lesions. In the manuscript "Case report: targeted sequencing improves the diagnosis of multiple synchronous lung cancers", authors presented a report of 3 lung adenocarcinoma cases who presented with 2 lesions, with improved diagnosis based on targeted sequencing covering driver genes.

Couple questions are required to be answered before it will be accepted.

(1) The targeted sequencing was the crucial topic in the study. Please make a brief introduction.

Response: Thank you for your precious comment and advice， we added the introduction of targeted sequencing see page4 lines 76-82.

(2) It was proposed to add related reference (DOI: 10.21037/tcr-22-2225) about the drive genes in lung adenocarcinoma.

Response: Thank you for your precious comment and advice， we added the reference see page10 lines 269-271.

(3) The figure 1A and 1B was not clearly enough. Please replace them with new.

Response: Thank you for your precious comment and advice, we have modified the figure1A and 1B see Figure 1-revised.

(4) Compared to conventional diagnostic techniques, what were the advantages of targeted sequencing for lung cancer? Please state in the discussion.

Response: Thank you for your precious comment and advice, we added the advantages of targeted sequencing see page 7 lines 176-179.

(5) Whether the combination targeted sequencing containing driver genes with conventional diagnostic techniques will be better than single targeted sequencing diagnosis for lung cancer? Please state in the discussion.

Response: Thank you for your precious comment and advice, we added the discussion of targeted sequencing with driver genes vs single gene see page 7 lines179-183

(6) What is the prospect of the developed novel technique in the study in the future? Please state in the discussion.

Response: Thank you for your precious comment and advice, we added the discussion of the prospect of the developed novel technique see page 7 lines 184-185 and 188-189.