

Peer Review File

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Reviewer A

First, the abstract needs some revisions. The background only indicates the knowledge gap but did not describe the unique clinical contribution of this case report. In the case presentation, the authors need to provide more detailed information for excluding the possibility of the coexistence of NSCLC and SCLC. Please report the findings on the biomarkers, the follow up duration, long-term prognosis of this case, and the efficacy and safety outcomes of atezolizumab treatment. The conclusion could be more detailed for the clinical implications of the findings, i.e., clinical indications for re-biopsies.

Authors' response: Thank you for your suggestion. **In the background**, we added the unique clinical contribution of this case report (see Page 2, line 36-38).

In July 2019, the patient was diagnosed with ALK-positive stage IVB NSCLC, received alectinib and responded to alectinib. It was not until more than 7 months later that a cranial MRI showed brain metastases. Of course, at the time of initial diagnosis, the biopsy revealed only NSCLC components, without any evidence of SCLC. Therefore we believe that these findings did not support the theory that the 2 tumor subtypes coexist. **In the case presentation**, we added the above description (see Page 2, line 42-43). In addition, we added the biomarkers, long-term prognosis of this case, and the efficacy and safety outcomes of atezolizumab treatment (see Page 2, line 48-55). **In the conclusion**, the first thing we emphasize is the clinical value of re-biopsy in such patients (see Page 2, line 56-57).

Second, in the introduction of the main text, please have more detailed review on the difficulties for the management of SCLC transformed from NSCLC and analyze the potential reasons. Based on this, please describe the clinical question that could be answered by this case report. It is very arbitrary to describe "NSE and other biomarkers as predictors of SCLC transformation" since this case report cannot answer this clinical question.

Authors' response: First, we strongly agree with the reviewer. The management of NSCLC into SCLC is difficult. This part is also described in our manuscript. We just put it in the discussion section (see Page 6, line 160-173). In the introduction section, we would like to focus on the rarity of SCLC transformed from ALK-positive NSCLC, and the treatment of this subset of patients for whom there are currently no standard treatment regimens and published cases with poor prognosis. Thus we draw our case, the patient received combined immunotherapy, and the prognosis is good.

Third, in the case presentation, a timeline figure is needed to briefly describe the early clinical presentations, diagnosis of NSCLC, findings from physical examinations, history of major medical conditions, follow up procedures, the progression of cancer,

reasons for suspension of the alectinib, i.e., severe adverse events, and detailed causes of deaths, i.e., heart failure?

Authors' response: A timeline does provide a clear and rapid understanding of the patient's treatment and key events. Therefore, according to review's suggestion, we added figure 3G for the timeline (see Page 16, Figure 3G).

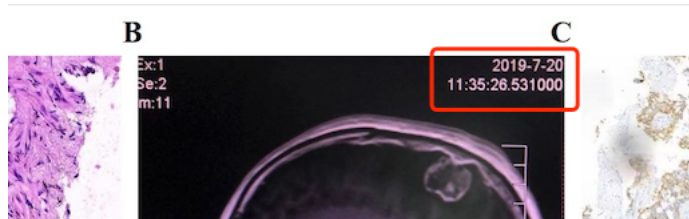
Fourth, the discussion is still repeating the main findings. I suggest the authors to compare the clinical characteristics and treatment strategies of this case with prior cases in the literature and analyze why the case had a relative good short-term prognosis.

Authors' response: This is a very good suggestion. We have added comparative data for this subset of cases (Table 1, see Page 17). As shown in Table 1, it is possible that the earlier the treatment, the better the prognosis. Because the more advanced patients, patients with poor physical fitness. On the other hand, combined immunotherapy may be the best choice for these patients. Of course, it will need to be confirmed in more cases in the future.

Reviewer B

1. Figure 1

- Please provide the magnification in the legend for 1A and 1C.
- Please explain MRI and ALK in the legend.
- Please remove or mask any information which may reveal the patient's privacy.



Author responses: Figure 1 legend modified as follows: **Figure 1** The patient's initial diagnosis. (A) Hematoxylin and eosin staining of the left lung (100×). (B) Magnetic resonance imaging (MRI) from initial diagnosis on July 20, 2019 showed brain metastases. (C) Immunohistochemistry showed that the lung puncture specimen was positive for anaplastic lymphoma kinase (ALK, 20×) (see Page 15, line 452-455). Figure 1 has also been revised and uploaded.

2. Figure 2

Please remove or mask any information which may reveal the patient's privacy.

Author responses: Thank you for your reminding.

3. Figure 3

- Please translate the Chinese into English.
- Please provide the magnification in the legend for 3C

c) Please explain ALL the abbreviations of the figure in the legend. Such as CT, NSCLC, IHC, etc.

d) Is there any meaning for below blue arrow in Figure 3E? Please indicate the meaning in the legend.

Author responses: Thank you for your reminding. We have added the magnification in the legend for 3C and the full names of all the abbreviations (see Page 16, line 465-472). In addition, the Chinese in the Figure 3 has been processed. Blue arrow indicates the tumor (see page 16, line 465-469).

4. Table 1:

Please add unit for Age.

Table 1 Summary of cases of SCLC transformed from ALK-posit

<u>Patient No.</u>	<u>Sex</u>	<u>Age</u>	<u>Origin</u>	<u>CNS metastasis*</u>

Author response: Thank you for your reminding. The unit for Age is year. We added it in Table 1 (see page 17).

5. Acknowledgment

We found that the abstract has been presented at IASLC 2022 World Conference on Lung Cancer, please provide a corresponding statement in the acknowledgment section.

Author responses: Thank you for your suggestion, we have added in Acknowledgment (see Page 11, line 342).