Peer Review File

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Reviewer A

Thank you for taking the time to review our manuscript. We appreciate your thoughtful feedback and constructive comments.

Comment 1: Immunoglobulin Deficiency: It would be beneficial for the report to investigate the potential correlation between the immunoglobulin deficiency and the observed drug resistance. Is there evidence suggesting that this deficiency can influence carcinogenesis or the emergence of specific genetic mutations?
Reply 1: We couldn't find any information on immunoglobulin deficiency and resistance to ALK inhibitor in lung cancers.

But we found that cancer is the leading cause of death for both children and adults with Primary Immunodeficiency with the likelihood of developing cancer ranging from 4% to 25%. Non-Hodgkin's lymphomas are the most common cancer type, making up 60% of cases[1]. However, there is no increased risk of solid cancer[2].

We couldn't find information on the specific link between primary immune issues and specific genetic mutations.

1. Filipovich, A. H., Mathur, A., Kamat, D. & Shapiro, R. S. Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res.* **52**, 5465s–5467s (1992).
2. Mayor, P. C. *et al.* Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry. *J. Allergy Clin. Immunol.* **141**, 1028–1035 (2018).

Changes in the text: We didn't change the text because we couldn't find any information on immunoglobulin deficiency and resistance to ALK inhibitor in lung cancers.

Comment 2: Association with Malignant Pleural Mesothelioma (MPM): There exist studies that indicate a link between MTAP deficiency and MPM. Was a differential diagnosis based on the immunostaining of tissues achievable in this context?
Reply 2: There wasn't any differential diagnosis in this context.
Changes in the text: see page, line: No differential diagnosis.

Comment 3: Medical History: Despite the patient's relatively young age of 39, it would be pertinent to include any history of exposure to known risk factors, such as asbestos inhalation. Such details can provide invaluable context, enhancing our understanding of the case.
Reply 3: There is no evidence of exposure to external known risk factors in the patient's medical history.
Changes in the text: The patient wasn't exposed to known risk factors.

Comment 4: Gene Mutations and Primary Resistance: The identified genetic alterations, namely the deletion of MTAP exons 6-8, deletions of CDKN2A and CDKN2B, the Q2274 mutation in the EP300 gene, and the E285K mutation in exon 8 of the TP53 gene, could shed light on the observed primary resistance. A comprehensive analysis of each of these mutations is crucial to understand their potential roles in inducing drug resistance.
Reply 4: Each identified genetic alterations are described in the literature as responsible of primary resistance to TKI.[3–5]

3. Lim, S. M. *et al.* Molecular landscape of osimertinib resistance in patients and patient-derived preclinical models. *Ther. Adv. Med. Oncol.* **14**, 175883592210791 (2022).
4. Zhang, Y.-C. *et al.* Analysis of resistance mechanisms to abivertinib, a third-generation EGFR tyrosine kinase inhibitor, in patients with EGFR T790M-positive non-small cell lung cancer from a phase I trial. *EBioMedicine* **43**, 180–187 (2019).
5. Jiang, J. *et al.* Coexistence of p16/CDKN2A homozygous deletions and activating EGFR mutations in lung adenocarcinoma patients signifies a poor response to EGFR-TKIs. *Lung Cancer* **102**, 101–107 (2016).

Changes in the text: We added in the discussion "Those co-mutations are described in the literature as responsible of primary resistance to TKI and may explain the ALK inhibitor resistance observed in this case[18]–[20]". See page 3-4, line 102-103.

Reviewer B

We would like to express our gratitude for taking the time to review our manuscript. Your feedback helped us improve our article.

Comment 1: In previous reports, the KLC1/ALK fusion gene has been associated with differentiation towards neuroendocrine tumors such as LCNEC and SCLC. In this case, it is recommended to address whether there is any histological or immunohistochemical evidence of differentiation towards neuroendocrine tumors. This could provide valuable insights into the tumor's biological behavior.

Reply 1: A pulmonary biopsy was achieved, but unfortunately, the patient passed away before we had the results. Our objective was to confirm whether there had been any transformation in Small Cell Lung Cancer. The biopsy confirmed that it was a non-small cell Lung cancer ALK +.
Changes in the text: We added in the case presentation "A pulmonary biopsy was performed shortly before the patient's passing, confirming that there had been no transformation in a Small Cell Lung Cancer.". See page 3, line: 76-77.

Reviewer C

Thank you for your time and effort in reviewing our work. We want to express our gratitude for your invaluable, thoughtful comments.

Comment 1: pure adenocarcinoma or mixed histo ?
Reply 1: It was a pure adenocarcinoma.

Comment 2: was ALK diagnosis made on pleural core biopsy or cyto?
Reply 2: ALK diagnosis was made on pulmonary biopsy.
Changes in the text: We added "The diagnosis was made on pulmonary biopsy" in the case description (see page 2, line 54-55).

Comment 3: And was IHC diffusely strongly positive?
Reply 3: The IHC was strongly positive (100% of cells).

Comment 4: Was tissue diagnosis FISH or NGS? If latter which panel?
Reply 4: The fusion transcripts were identified by NGS. The panel used was FusionPlex Lung,#SK0133, ArcherDx.
Changes in the text: We added in the case description : "The diagnosis was made on pulmonary biopsy and the fusion transcripts were identified by a technique of New Generation Sequencing using the panel FusionPlex Lung, #SK0133, ArcherDx." (see page 2, line 54-55).

Comment 5: Was rebiopsy performed at primary resistance to alectinib/brig in case phenotypic transformation? If not, why not? ctDNA will not assist here. Noted however underperformed on platnum challenge.
Reply 5: A pulmonary biopsy was achieved, but unfortunately, the patient passed away before we had the results. Our objective was to confirm whether there had been any transformation

in Small Cell Lung Cancer. The biopsy confirmed that it was a non-small cell Lung cancer ALK +.
Changes in the text: We added in the case presentation “A pulmonary biopsy was performed shortly before the patient's passing, confirming that there had been no transformation in a Small Cell Lung Cancer.”. See page 3, line: 76-77.

Comment 6: First ctDNA assay only revealed TP53 variant, not ALK fusion. Noted a DNA panel, however which one e.g. validated to capture ALK/which ALK fusions?
Reply 6: We used the FoundationOne Liquid CDx and the LiquidPlex ctDNA panel.

Comment 7: I would recommend also a word in discussion on the performance of ALK-inhibtitors/TKI's in the literature in immunocompromised individuals impacting primary resistance.
Reply 7: We couldn’t find anything in the literature on immunodeficiency disease impacting primary resistance.