

Peer Review File

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Reviewer A

Comment 1: "In my opinion the sentence "Some limitations to our report include our patient's poor prognosis and advanced staging on initial presentation, which restricted the use of further investigational therapies." should be deleted. The PS of the patient is not a limitation of your case report but the situation of the patient."

Reply 1: We have removed this sentence from our manuscript and agree that it was not a limitation. Instead, we use the first paragraph of our discussion to highlight the patient's condition as a "key feature" and how our case report serves as an example of the difficulty in managing Non-Small Cell Adenocarcinoma without driver mutations.

Changes in the Text:

- Removed Sentence on Pg 6, Line 1-3

Comment 2: "The discussion is divided in two clear parts: the discussion on the cancer treatment and the discussion on the route of skull metastases acquisition. In my opinion the second part could be of more interest to the readers of the journal and should gain more weight in your revision of the manuscript."

Reply 2: In our original draft of the manuscript, we included one paragraph about the route of skull metastases. In order revision, we delve into an anatomical and physiological evaluation of the route of metastasis. We contrast lung cancer with other types of cancers in described routes of metastasis and we believe giving this additional weight to the topic will entertain the curiosity of our readers while completing our case report. We have also cited 3 additional

resources regarding the epidemiology, pathophysiology, and distribution of calvarial and brain metastases.

Changes in the Text:

- Insert Pg 7, Line 18 - Pg 8, Line 7
- “In general, calvarial metastases, found in 15-25% of all cancer patients, occurs through three well-identified routes: (1) via direct extension through cranial foramina, (2) retrograde seeding through Batson venous plexus, or (3) hematogenous spread (13). Hematogenous spread appears to be the most common mechanism for brain metastasis as evidenced by the predilection of brain metastasis to appear at the junction of white and gray matter (14). This area contains smaller diameter blood vessels that can stagnate tumor cells. Additionally, brain metastases are more common in areas with less blood flow compared to relative weight. As such, 80 percent of brain metastasis occurs to the cerebral hemispheres with “watershed area”, while only 15 and 5 percent occur to the cerebellum and brainstem, respectively (15). Lastly, the type of primary cancer retains a role in establish the area of metastases. Metastases from lung cancers are unique in being equally distributed throughout the brain, while prostatic, uterine, gastrointestinal, and breast tumors are most commonly found to metastasize to the posterior fossa due to cell surface properties of these tumor cells (16).”

Reviewer B

***Comment 3:** “Skull metastasis of lung cancer itself would be so uncommon. The presentation of this case was impressive, but the rarity or novelty of this case seems still unclear. What are the clinical lessons or implications the authors can draw from*

this case? The authors should clarify this point.”

Reply 3: In our revised manuscript, we bring more attention to the clinical lessons and implications that readers can draw from this case. We added additional citations that show lack of antemortem brain metastasis diagnoses compared to autopsy report to shine light on the amount of misdiagnosis that are present. For example, we site a study of autopsy reports that found brain metastases in lung cancer patients are more than three times present than actually diagnosed. Additionally, we delve into the clinical manifestations of brain metastases and explain diagnostic medical plans that can be carried out to accurately diagnose patient and improve medical outcomes.

Changes in the Text:

- Insert Pg 8, Line 16 - Pg 9, Line 6
- “The clinical manifestations of brain metastasis are profound and can involve focal neurologic dysfunction, seizures, and strokes. While the cumulative incidence of brain metastases in patients with lung cancer is only noted to be 16 to 20 percent, there is reason to suggest that brain metastases are much more common than diagnosed. In a review of autopsy series, brain metastases were found in as many as 64 percent of patients dying from lung cancer (17). The clinical implication of this would be to be more vigilant in considering brain metastases in cancer patients with that presents with complaints of memory problems, mood or personality changes, new-onset seizures, and other common clinical manifestations of brain metastases. Additional testing with contrast enhanced magnetic resonance imaging (MRI) can help provide a diagnose. Survival of patient with brain metastases has also improved with systemic therapy and surgical advances. For example, stereotactic radiosurgery (SRS) has been more widely available and is regarded as more efficacious and safer than whole brain radiation therapy (WBRT) (18).”

***Comment 4:** The aggressiveness of the tumor seems to be one of the features in this relatively young female patient. The additional descriptions on pathological evaluations, not just showing it as EGFR/ALK negative adenocarcinoma, of this case would improve comprehensibility of this case report.*

Reply 4: To improve the comprehensibility of our case report, we further described the pathological evaluation that was completed. We included more extensive information to give readers about the exacted techniques, such as mutation analysis, Fluorescence In Situ Hybridization (FISH), and immunohistochemistry (IHC), that were used to evaluate our patient. We believe this would add more information regarding the work-up of our patient and provide value by mentioning factors other than EGFR/ ALK that were considered in this case report.

Changes in the Text:

- Addition of “The tissue was sent for pathological evaluation. Mutation analysis for EGFR mutations and BRAF V600 mutations were negative. Additionally, a Fluorescence In Situ Hybridization Test (FISH) using two multiplex problem stain procedures showed no evidence of a rearrangement of ALK (2p23) and ROS1 (6q22). Lastly, PD-L1 testing by immunohistochemistry (IHC) resulted in no PD-L1 expression or Tumor Proportion Score (TPS) < 1%.” on Pg 4, Line 10

***Comment 5:** “The authors should clearly present TNM staging for this case.”*

Reply 5: We agree that TNM staging is important when mentioning cancer and have included the TNM staging. This will clearly define the severity of lung adenocarcinoma and give prognostic value for readers.

Changes in the Text:

- Added: “T4N3M1c” on Pg. 3, Line 21

Comment 6: *“Discussion: The explanations on the results from clinical trial for ICI monotherapy or chemoimmunotherapy seems to be redundant and unnecessary for this case report. Rather, the authors should focus on the value of this case report. Why this case report needs to be published. This point is essential to justify publication of this manuscript.”*

Reply 6: **We revised our manuscript to focus on the values of this case report and added more information to solidly the novelty of the case report and what it offers to readers. We expand upon the lack of information regarding routes of brain metastases, the clinical information that is often missed in diagnosing patients, and how we can better evaluate patients to improve their outcomes.**

Changes in the Text:

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- “In general, calvarial metastases, found in 15-25% of all cancer patients, occurs through three well-identified routes: (1) via direct extension through cranial foramina, (2) retrograde seeding through Batson venous plexus, or (3) hematogenous spread (13). Hematogenous spread appears to be the most common mechanism for brain metastasis as evidenced by the predilection of brain metastasis to appear at the junction of white and gray matter (14). This area contains smaller diameter blood vessels that can stagnate tumor cells. Additionally, brain metastases are more common in areas with less blood flow compared to relative weight. As such, 80 percent of brain metastasis occurs to the cerebral hemispheres with “watershed area”, while only 15 and 5 percent occur to the cerebellum and brainstem, respectively (15). Lastly, the type of primary cancer retains a role in establish the area of metastases. Metastases from

lung cancers are unique in being equally distributed throughout the brain, while prostatic, uterine, gastrointestinal, and breast tumors are most commonly found to metastasize to the posterior fossa due to cell surface properties of these tumor cells (16).”

Insert Pg 8, Line 16 - Pg 9, Line 6

- “The clinical manifestations of brain metastasis are profound and can involve focal neurologic dysfunction, seizures, and strokes. While the cumulative incidence of brain metastases in patients with lung cancer is only noted to be 16 to 20 percent, there is reason to suggest that brain metastases are much more common than diagnosed. In a review of autopsy series, brain metastases were found in as many as 64 percent of patients dying from lung cancer (17). The clinical implication of this would be to be more vigilant in considering brain metastases in cancer patients with that presents with complaints of memory problems, mood or personality changes, new-onset seizures, and other common clinical manifestations of brain metastases. Additional testing with contrast enhanced magnetic resonance imaging (MRI) can help provide a diagnose. Survival of patient with brain metastases has also improved with systemic therapy and surgical advances. For example, stereotactic radiosurgery (SRS) has been more widely available and is regarded as more efficacious and safer than whole brain radiation therapy (WBRT) (18).”

Reviewer C

Comment 7: “The case should be better described including the technique and dose of RT and chemotherapy.”

Reply 7: The technique and dosing of radiotherapy was important in managing our patient and we agree with this comment. We have added a table to our case report to delve into the specifics of the treatment. We included the “Treatment Site” and with the more information about the dosing of radiation therapy that was administered. This will provide readers with more information about the management of our patient and show a better clinical picture of this case presentation.

Changes in the Text: Addition of “Table 1”, Referenced on Page 4, Line 18.