Peer Review File

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Reviewer Comments

General Impression:

The manuscript named "Esophagomediastinal fistula during durvalumab plus tremelimumab with chemotherapy in angiotensin-converting enzyme 2-positive non-small cell lung cancer" presents a unique and highly relevant case report. This report is particularly timely given the ongoing global impact of the COVID-19 pandemic and its significant intersections with cancer treatment, particularly for immunocompromised patients. The integration of COVID-19 considerations into cancer therapy is an area of intense interest and research, making this manuscript especially pertinent in 2024 as we continue to navigate the pandemic's long-term effects on healthcare. The manuscript is well-structured and provides detailed clinical insights, which are invaluable for clinicians managing similar cases. The case highlights the complex interplay between immune checkpoint inhibitors (ICIs) and viral infections, shedding light on both the therapeutic potentials and the severe adverse effects that can arise. The discussion on immune-related adverse events (irAEs) in the context of COVID-19 is particularly interesting and emphasises the need for careful patient monitoring and management.

However, there are areas where clarity and depth can be improved to enhance the overall quality and impact of the manuscript. Specifically, the organisation of the case description could be better structured to highlight the chronological progression of the patient's condition and treatment, thereby improving readability. Additionally, the depth of the literature context should be expanded to include more recent studies and data from 2023 and 2024, providing a current perspective on the topic. The exploration of speculative mechanisms, such as the potential role of SARS-CoV-2 as an oncolytic virus, is intriguing but requires more robust support. Providing a more detailed discussion of these mechanisms, backed by the latest research, would strengthen the manuscript. Furthermore, the detail in figure captions should be enhanced to guide readers through the key observations and their relevance to the case, ensuring that the visual data complements the narrative effectively.

In conclusion, while the manuscript presents a highly relevant and well-documented case, addressing these areas of improvement will significantly enhance its readability, scientific rigour, and overall impact on the field. The case report offers valuable insights into the challenges and opportunities presented by the intersection of COVID-19 and cancer treatment, and with these enhancements, it will make a strong contribution to the literature.

Major Comments:

Comment 1.

• Clarity in Background:

o In the background section (lines 21-22), clarify the term "driver mutations" by specifying the genes typically involved, such as EGFR or ALK. This helps readers who may not be familiar with the terminology. The term "no driver mutations" could be revised to "no driver mutations, such as those in EGFR or ALK genes ".

Reply 1.

Thank you for your valuable comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 3, line 40–41)

no driver mutations such as those in EGFR or ALK genes

Comment 2.

o The introduction provides a solid background but could be enriched with more specific data on the prevalence and management challenges of NSCLC in the context of the COVID-19 pandemic. Include recent statistics or studies that underline the significance of studying ICIs in the COVID-19 era (lines 68-70). Add data such as, "Recent statistics indicate that NSCLC remains a leading cause of cancer-related mortality, with the COVID-19 pandemic introducing new challenges in managing these patients (references)."

Reply 2.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 6, line 87–89)

Recent statistics indicate that non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality, with the COVID-19 pandemic introducing new challenges in managing patients with NSCLC (1, 2).

• Case Description: The detailed description is commendable, but the timeline of events can be made clearer.

Comment 3.

o Consider breaking down the complications and treatment interventions into bullet points or separate sentences for better clarity and readability (lines 20-30). Instead of listing all complications in a single sentence, break it down: "The patient experienced multiple complications including: (1) oesophageal mediastinal fistula, (2) severe irAEs such as grade 3 colitis, (3) COVID-19 and Candida albicans infections, (4) cytokine release syndrome, and (5) myocarditis. Treatment interventions included high-dose steroids, antifungal therapy, mechanical support in the intensive care unit, and haemodialysis."

Reply 3.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 3, line 43–46)

The patient experienced multiple complications including: (1) esophageal mediastinal fistula, (2) severe irAEs such as grade 3 colitis, (3) COVID-19 and *Candida albicans* infections, (4) cytokine release syndrome, and (5) myocarditis. Treatment interventions included high-dose steroids, antifungal therapy, mechanical support in the intensive care unit, and hemodialysis.

Comment 4.

o Even better would be using a table or timeline diagram to summarise the key events, treatments, and outcomes in chronological order (lines 83-117). Create a timeline table that highlights significant events, treatments, and complications, such as the onset of symptoms, treatment dates, development of complications, and outcomes.

Reply 4.

Thank you for your comment. We added a supplementary table as you indicated.

Change in the text:

We have modified our text as advised (see Page 8, line 141–142)

A brief progress table is presented as Supplementary Table 1.

Comment 5.

• Rationale and Knowledge Gap: Provide more context on the incidence and management of irAEs in patients with NSCLC receiving ICIs to set a clearer stage for the case (lines 73-75). After "The global COVID-19 epidemic has further complicated cancer treatment with ICIs," add "with studies indicating an increase in the incidence and severity of irAEs in patients undergoing such treatments."

Reply 5.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 6, line 94–95)

The global COVID-19 epidemic has further complicated cancer treatment with ICIs, with studies indicating an increase in the incidence and severity of irAEs in patients undergoing such treatments.

• Clarity and Structure in the Case Presentation:

Comment 6.

o The manuscript is generally well-organised, but certain sections could benefit from improved clarity. For example, the case description section is detailed but could be better structured to highlight the chronological progression of the patient's condition and treatment. Consider using subheadings within the case presentation to organise the information more clearly as well as to improve readability and the overall flow (line 83). Add subheadings such as "Initial Presentation," "Treatment Regimen," "Complications," and "Outcomes" to guide the reader. Examples (lines 83-117):

1. Initial Presentation: "A 44-year-old man with no previous medical history visited the hospital because of an oesophageal transit disorder. The patient underwent endobronchial ultrasound-guided transbronchial needle aspiration..."

2. Treatment Regimen: "The patient received durvalumab (1,500 mg/body, day 1) plus tremelimumab (75 mg/body, day 1) and chemotherapy comprising carboplatin..."

3. Complications: "On day 8 of treatment, the patient developed grade 2 liver dysfunction... Fungalemia may have been a hematogenous infection..."

4. Outcomes: "Two months after CRS onset, the patient developed cytomegalovirus infection... More than six months after the beginning of treatment, CT showed tumour remission..."

Reply 6.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 6, line 104; Page 7, lines 112 and 116.)

• Comparative Analysis:

Comment 7.

o Include a comparative analysis with previous reports of similar complications in NSCLC patients treated with ICIs to highlight the novelty and significance of your findings (lines 137-138). Add a paragraph discussing previous reports: "Similar complications have been reported in other cases of NSCLC treated with ICIs. For instance, tracheamediastinal and tracheoesophageal fistulas have been observed... (references). This comparison highlights the unique aspects of the current case and its implications for clinical practice."

Reply 7.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 9, line 162–165.)

Similar complications have been reported in other cases of NSCLC treated with ICIs. For instance, tracheamediastinal and tracheoesophageal fistulas have been reported as rare complications of ICI therapy in advanced lung cancer (10, 11).

Comment 8.

o The discussion section provides a good overview of relevant literature but lacks a critical analysis of how this case report contributes to the existing body of knowledge. However, could you elaborate on how the findings of this case report compare with previous reports of similar complications in NSCLC patients treated with ICIs?

Reply 8.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 9–10, line 165–171.)

In both previous reports, other factors such as chemoradiotherapy, mechanical irritation with esophageal stents, and delayed wound healing with angiogenesis inhibitors were considered as potential factors for fistula formation; however, the fistula formed 6–10 weeks after ICI administration, and a temporal causal relationship with the other factors could not be established, making the ICI a suspect drug. In the present case, although cytotoxic chemotherapy was administered concurrently, the course of treatment is consistent with previous reports that ICIs are most likely to be involved in fistula formation.

• Speculative Mechanisms:

Comment 9.

o Provide additional references and a more detailed discussion on the potential mechanisms by which SARS-CoV-2 might enhance antitumor immunity (lines 149-160). Expand the discussion: "The hypothesis that SARS-CoV-2 may act as an oncolytic virus is supported by several studies. For example, studies have shown that oncolytic viruses can induce cell death and cancer antigen release (Melcher et al., 2021). Additionally, SARS-CoV-2's infection mechanism via ACE2 expression could further support this hypothesis (Hoffmann et al., 2020)."

Reply 9.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 10–11, line 184–189.)

The hypothesis that SARS-CoV-2 may act as an oncolytic virus, which selectively kills cancer cells and boosts immune response, is supported by several studies. For example, studies have shown that oncolytic viruses can induce cell death and cancer antigen release (13). Additionally, SARS-CoV-2 infection mechanism via ACE2 expression could further support this hypothesis (14). Recently, a combination therapy involving oncolytic viruses and ICIs has been developed in clinical settings, with excellent therapeutic efficacy (15).

Comment 10.

o The hypothesis that SARS-CoV-2 may act as an oncolytic virus and contribute to antitumor effects is fascinating but requires more robust support. Are there any existing preclinical or clinical studies that support this hypothesis? If so, please reference them to strengthen your argument.

Reply 10.

Thank you for your comment. Repeated searches have been conducted since the paper was written, but no corresponding paper has been found.

We have modified our text as advised (see Page 11, line 192–193.)

As similar cases have not yet been reported, continued hypothesis testing is required in the future.

• Discussion: The discussion on irAEs and their management is informative but somewhat repetitive. Streamline the discussion to avoid repetition and focus on novel insights provided by this case. Remove repetitive statements and consolidate information about the management of irAEs to focus on the novel aspects of the case (lines 125-160).

• Broader Implications: Emphasise specific recommendations for clinical practice and future research (lines 163-165).

Comment 11.

o Highlight specific recommendations for clinical practice and future research directions based on the case findings. Consider revising to: "Clinicians should carefully monitor the presence of COVID-19 during ICI therapy, as it may be associated with severe irAE development or unexpectedly enhanced antitumor effects. Future research should explore the mechanisms by which viral infections influence tumour immunity and investigate potential therapeutic strategies that leverage these interactions."

Reply 11.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 11, line 196–199.)

Clinicians should carefully monitor the presence of COVID-19 during ICI therapy, as it may be associated with severe irAE development or unexpectedly enhanced antitumor effects. Future research should explore the mechanisms by which viral infections influence tumor immunity and investigate potential therapeutic strategies that leverage these interactions.

Comment 12.

o How do you foresee the findings of this case influencing future therapeutic strategies for NSCLC patients, particularly in the context of ongoing or future pandemics (lines 163-165)? Consider discussing potential changes in monitoring protocols, treatment adjustments, or research focuses that might arise from the findings of this case.

Reply 12.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 11, line 196–199.)

Clinicians should carefully monitor the presence of COVID-19 during ICI therapy, as it may be associated with severe irAE development or unexpectedly enhanced antitumor effects. Future research should explore the mechanisms by which viral infections influence tumor immunity and investigate potential therapeutic strategies that leverage these interactions.

• Expanded Captions in the Figure and Visuals: The figures would benefit from more detailed captions to guide the reader through the key observations. Provide detailed captions for the figures to enhance understanding (Figures 1 and 3). Expand the figure captions to include explanations of what each image shows and its relevance to the case.

Comment 13.

o Figure 1: Revise the caption to: "(A) Before starting chemotherapy, the tumour in the mediastinum was observed to be compressing the bronchial wall and was partially exposed to the oesophagus. (B) After 42 days of chemotherapy, the tumour disappeared; however, an air space extended from the oesophagus into the mediastinum. Endoscopy revealed a fistula at the same site. (C) Endoscopic examination showing that the fistula was covered by the stent immediately after placement of the oesophageal stent. (D) After removal of the oesophageal stent, CT revealed the absence of a tumour. Endoscopy revealed a small dimple at the site of the fistula."

Reply 13.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 14, line 256–262.)

(A) Before starting chemotherapy, the tumor in the mediastinum was observed to be compressing the bronchial wall and was partially exposed to the esophagus. (B) After 42 days of chemotherapy, the tumor disappeared; however, an air space extended from the esophagus into the mediastinum. Endoscopy revealed a fistula at the same site. (C) Endoscopic examination showing that the fistula was covered by the stent immediately after placement of the esophageal stent. (D) After removal of the esophageal stent, CT revealed the absence of a tumor. Endoscopy revealed a small dimple at the site of the fistula.

Comment 14.

o Figure 3: Ensure to explain the significance of ACE2 expression in tumour cells and its relevance to the case.

the fistula."

Reply 14.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 14, line 274– Page 15, line 276.)

H&E staining of the biopsy specimen revealed tumor cells (A) expressing ACE2 on the cell membrane (B), which is critical in the infection mechanism of SARS-CoV-2, suggesting that SARS-CoV-2 also infected tumor cells.

Minor Comments:

Comment 15.

• Terms such as "driver mutations" and "oncolytic viruses" are used but not defined. Briefly explain these terms when first mentioned to ensure clarity for all readers.

Reply 15.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 7, line 110–111 and Page 10, line 184–185.)

negative for driver mutations such as those in EGFR or ALK genes, …

… an oncolytic virus, which selectively kills cancer cells and boosts immune response, is supported by several studies.…

Comment 16.

• The conclusion is concise but could better emphasise the broader implications of the findings.

Reply 16.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (See Page 11, line 196–199.)

Clinicians should carefully monitor the presence of COVID-19 during ICI therapy, as it may be associated with severe irAE development or unexpectedly enhanced antitumor effects. Future research should explore the mechanisms by which viral infections influence tumor immunity and investigate potential therapeutic strategies that leverage these interactions.

Comment 17.

• The ethical statement and informed consent details are adequately addressed. Ensure that any identifying information of the patient is thoroughly anonymised to maintain confidentiality. Ensure all personal identifiers are removed or anonymised in line with ethical guidelines (lines 118-122).

Reply 17.

Thank you for your comment. Anonymization was checked and found to be OK.

Recommendations:

Comment 18.

• Clarify and structure the case description with subheadings.

Reply 18.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 7, line 104, line 112 and line 116.)

Comment 19.

• Enhance the discussion with comparative analysis and detailed exploration of speculative mechanisms.

Reply 19.

Thank you for your comment. We have corrected the text as you indicated.

Comment 20.

• Expand figure captions for better reader guidance.

Reply 20.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (see Page 14, line 274– Page 15, line 276.)

H&E staining of the biopsy specimen revealed tumor cells (A) expressing ACE2 on the cell membrane (B), which is critical in the infection mechanism of SARS-CoV-2, suggesting that SARS-CoV-2 also infected tumor cells.

Comment 21.

• Define key terms and ensure all patient information is anonymised.

Reply 21.

Thank you for your comment. We have corrected the text as you indicated.

Anonymisation was checked and found to be OK.

Change in the text:

We have modified our text as advised (see Page 7, line 110–111 and Page 10, line 184–185)

negative for driver mutations such as those in EGFR or ALK genes, …

… an oncolytic virus, which selectively kill cancer cells and boost immune response, is supported by several studies.

Comment 22.

• Emphasise broader implications in the conclusion.

Reply 22.

Thank you for your comment. We have corrected the text as you indicated.

Change in the text:

We have modified our text as advised (See Page 11, line 196–199.)

Clinicians should carefully monitor the presence of COVID-19 during ICI therapy, as it may be associated with severe irAE development or unexpectedly enhanced antitumor effects. Future research should explore the mechanisms by which viral infections influence tumor immunity and investigate potential therapeutic strategies that leverage these interactions.