Immune Reconstitution Inflammatory Syndrome After the Initiation of Antiretroviral Therapy in an AIDS-Stage Patient: A Case Report," submitted for consideration by your prestigious journal.

Response to reviewers

Attached to this letter is the new version of the manuscript with the implemented changes.

The implemented changes were the following, detailed segment by segment, for your review.

Changes made to the manuscript:

1. Title

Original: "Early Immune Reconstitution Inflammatory Syndrome After Initiation of ART in a Patient with AIDS-Stage HIV"

Change: Adjusted to a more cautious form, emphasizing "possible IRIS" and adding the concept of early onset, while maintaining the case report structure.

Early-Onset Immune Reconstitution Inflammatory Syndrome After the Initiation of Antiretroviral Therapy in an AIDS-Stage Patient: A Case Report

Reason: The reviewers requested not categorically state that it was IRIS without definitive support and reflect the possibility of early-onset IRIS.

2. Summary

Main adjustments:

1. Added shorter wording introducing the context of IRIS and the possible early presentation.

2. Include the explicit goal of describing a "possible case of IRIS" rather than absolute confirmation.

3. Emphasized the need to rule out other infections, to address criticism that persistent fever could be due to other causes.

Reason: Reviewers requested that the summary not sound like a definitive conclusion and that it be clear that this is a case report.

3. Introduction

Main adjustments:

1. Added a paragraph explaining that IRIS can be triggered not only by opportunistic pathogens but also by autoimmune or neoplastic diseases.

2. The frequency was reaffirmed (10-25% in CD4 <50 cells/μL) and citations to recent literature were included.

3. The possibility of IRIS was explicitly mentioned even in the first week of ART.

Reason: To respond to criticisms about the "regular presentation" of the introduction and expand information on IRIS in other contexts.

4. Case presentation (Methodology/Clinical description)

Main adjustments:

1. Treatment chronology: It was detailed that the patient was already receiving meropenem and vancomycin, and that amphotericin B was added on the second day due to suspected histoplasmosis. In addition, the start date of ART (day 1) and TMP-SMX were specified.

2. Diagnostic support for pneumocystosis and candidiasis: PCR confirmation for Pneumocystis jirovecii and quantitative culture/DNA sequencing for Candida were mentioned.

3. Rationale for antibiotics (meropenem, vancomycin, ceftazidime-avibactam) and their duration, explaining why broad-spectrum coverage was maintained and the justification for discontinuing it after negative cultures.

4. Details of clinical status: Information about the transfer from a private hospital for financial reasons and confirmation of the ARDS diagnosis upon admission were added.

Reason: To address observations related to a lack of clarity in the timing of treatment, the justification for the use of broad-spectrum antibiotics, and confirmation of opportunistic diagnoses.

5. Discussion

Main adjustments:

1. The differentiation between IRIS and active/persistent infection was further elaborated, explaining the lack of clinical response to antibiotics and the negative culture results.

2. The use of corticosteroids (MEDURI Protocol) for severe pneumocystosis was mentioned, and it was discussed that it could also have influenced the IRIS.

3. More recent references documenting early IRIS (<2 weeks) were included, responding to the reviewers' request for a literature review from the last 5 years.

4. The Meintjes and French scales for IRIS were applied, and the clinical plausibility of the diagnosis was argued.

Reason: At the reviewers' request, the discussion on the pathophysiology of IRIS in severe pneumocystosis, the controversies surrounding the use of corticosteroids, and the importance of ruling out occult infections was expanded.

6. Conclusions

Main adjustments:

1. It was emphasized that early IRIS should be considered in patients with persistent fever and no response to antibiotics in the context of recent ART.

2. It was clearly stated that not all fever is due to a new infection and that multidisciplinary monitoring is key.

3. The importance of excluding other infectious causes before assuming IRIS was mentioned.

Rationale: The reviewers requested that the conclusions focus on "lessons learned" for clinical practice, rather than categorical or overly general conclusions.

7. References

Main adjustments:

1. The original citations (1–13) were retained, and recent references (14 and 15) were added to support the early presentation of IRIS.

2. The Vancouver-style format was standardized, including authorship, title, journal, year, and pagination.

3. The official source (Panel on Opportunistic Infections in Adults and Adolescents with HIV, 2023) was cited, which discusses IRIS and its management.

Reason: To conform to the journal's format, provide an updated bibliography from the last 5 years, and meet the reviewers' recommendations regarding consistency of style.

8. Ethical Aspects and Consent

Main adjustments:

1. A Declaration of Conflicts of Interest was included, indicating that none existed.

2. Explicit mention of the informed consent signed by the patient's family was added, guaranteeing confidentiality.

Reason: Some reviewers pointed out the need to clarify how informed consent was obtained and the existence (or lack thereof) of approval by an ethics committee.

9. General Tone and Terminology

Main Adjustments:

1. The term “HAART” was replaced with “ART” throughout the manuscript.

2. A more cautious tone was adopted in the diagnostic statement, using terms such as “possible IRIS” or “probable IRIS.”

3. The chronology of events was clarified (day 1, day 5, etc.) for greater consistency and precision.

Reason: To comply with a reviewer's suggestion not to use “HAART” and not to categorically state a diagnosis that could not be verified with formal criteria.

Summary of Changes

In each section (Abstract, Introduction, Case Presentation, Discussion, and Conclusions), key aspects were added or modified to address the reviewers' comments:

Greater chronological clarity

Detailed justification for treatments and cultures

Emphasis on the plausibility of early IRIS

Expansion of the literature

Compliance with ethical guidelines (informed consent)

Overall, the structure of the case report was strengthened, and concerns regarding the lack of evidence of other infections, the need for recent literature, and the inappropriate use of broad-spectrum antibiotics in a critically ill patient were addressed.