ISSN(O): 2320-5407 | ISSN(P): 3107-4928

International Journal of Advanced Research

Publisher's Name: Jana Publication and Research LLP

www.journalijar.com

REVIEWER'S REPORT

Manuscript No.: IJAR- 59129

Title: INVASIVE MUCORMYCOSIS IN PATIENTS WITH APLASTIC ANEMIA: REPORT OF TWO FATAL CASES.,

Recommendation:
Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality		✔		
Techn. Quality			✔	
Clarity			✔	
Significance	✔			

Reviewer's ID: Bilquees Hamza

Detailed Reviewer's Report

The manuscript titled **"INVASIVE MUCORMYCOSIS IN PATIENTS WITH APLASTIC ANEMIA: REPORT OF TWO FATAL CASES"** addresses a critically important, highly lethal clinical scenario: the management of invasive rhino-maxillofacial mucormycosis in patients suffering from severe idiopathic aplastic anemia. Mucormycosis is a fulminant, angioinvasive fungal infection predominantly caused by ubiquitous molds of the order Mucorales. While its occurrence is well-documented in poorly controlled diabetes mellitus and post-transplant populations, its emergence in the setting of aplastic anemia presents unique diagnostic and therapeutic challenges due to severe, persistent pancytopenia.

The authors present two clinical cases that illustrate the spectrum and devastating rapid progression of this infection:

1. **Case 1:** A 14-year-old patient with idiopathic aplastic anemia who developed a firm, painful right lower cheek swelling and trismus 5 days following the extraction of tooth 46. Computed tomography (CT) revealed an abscessed collection centered on the mandibular body. Despite diagnostic biopsy confirming mycelial filaments, initiation of liposomal amphotericin B (3 mg/kg/day), blood product transfusions, G-CSF administration, and surgical debridement with mandibular curettage, the patient suffered severe postoperative hemorrhage, progressive tissue necrosis, and died from fatal septic shock on postoperative day 5.
2. **Case 2:** A 40-year-old patient with idiopathic aplastic anemia presenting with a necrotic palatal ulceration with maxillary sinus and ethmoid involvement. Histopathological biopsy confirmed mucormycosis. The clinical course was rapidly complicated by fever, cough, and new pulmonary

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consolidation foci suggestive of disseminated disease, culminating in acute respiratory distress and death within the same week.

The manuscript succeeds in emphasizing the clinical dilemma faced by oral and maxillofacial surgeons and hematologists: standard clinical guidelines mandate aggressive, early surgical debridement alongside high-dose polyene antifungals. However, in severe aplastic anemia, profound neutropenia limits tissue healing and infection control, while severe thrombocytopenia dramatically elevates the risk of life-threatening surgical hemorrhage. The clinical photographs and radiological panels provided are highly illustrative. Nevertheless, to elevate the manuscript to the highest academic standard, several diagnostic, pharmacological, surgical, and textual aspects require refinement.

Suggestions for Improvement

1. Mycological and Histopathological Rigor

- **Histopathological Characterization:** In Section 2.2 and Figure 1C, the biopsy is noted to display "mycelial filaments". The description should be expanded to explicitly state the classic histological hallmarks of Mucorales: broad (5–20 μm diameter), ribbon-like, pauciseptate or non-septate hyphae exhibiting wide-angle (often 90°) branching.
- **Special Staining Procedures:** Clarify whether special fungal stains—such as Grocott's Methenamine Silver (GMS) or Periodic Acid–Schiff (PAS)—were utilized to highlight the fungal morphology in tissue sections.
- **Explanation of Negative Cultures:** In Case 1, parasitological/microbiological examination was reported as negative despite positive histology. The authors should briefly explain in the discussion that Mucorales hyphae are fragile and easily damaged during tissue homogenization/grinding in routine microbiology labs, which frequently leads to false-negative culture results.
- **Molecular Diagnostics:** State whether molecular methods (e.g., pan-fungal PCR or internal transcribed spacer [ITS] sequencing) or matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry were attempted or available to identify the specific genus (e.g., *Rhizopus*, *Mucor*, *Lichtheimia*).

2. Pharmacological and Therapeutic Management

- **Liposomal Amphotericin B Dosing:** The authors appropriately acknowledge in Section 3 that Case 1 received liposomal amphotericin B at 3 mg/kg/day, whereas global guidelines (such as the ECMM/MSG guidelines) recommend at least 5 mg/kg/day (and up to 10 mg/kg/day for central nervous system or extensive involvement). To improve clinical

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clarity, state in the Case 1 presentation whether renal function parameters (creatinine/eGFR) or drug availability influenced the initial dosing choice.

- **Adjunctive Immune Reconstitution Strategies:** The report mentions the use of granulocyte growth factors (G-CSF). The discussion could be strengthened by briefly addressing the controversial role of G-CSF alone versus granulocyte transfusions (GTX) or donor lymphocyte infusions in severe aplastic anemia with refractory fungal infections, as recovery of absolute neutrophil count (ANC) remains the single most critical determinant of long-term survival.
- **Maintenance/Salvage Triazole Therapy:** Discuss the potential role of second-generation triazoles (posaconazole or isavuconazole) as step-down or combination therapy, particularly in patients who cannot tolerate full-dose amphotericin B due to nephrotoxicity.

3. Surgical Strategy and Risk Mitigation in Severe Cytopenia

- **Surgical Debridement vs. Hemostatic Control:** In Case 1, surgical curettage was followed by significant bleeding and rapid spread of cutaneous necrosis. The authors should expand their discussion on the timing and extent of surgery when platelets are $15,000/\text{mm}^3$ and neutrophils are $10/\text{mm}^3$. Was conservative local debridement with topical hemostatic agents (e.g., tranexamic acid washes, fibrin sealants, oxidized cellulose) considered over extensive bone curettage?
- **Staging and Anatomical Extent:** Consider framing the extent of disease using established clinical staging systems for rhino-orbital-cerebral mucormycosis (ROCM) to help readers quickly gauge severity.

4. Completeness of Case Data and Manuscript Structure

- **Missing Details in Case 2:** As noted in the limitations section, specific antifungal dosages, surgical interventions (or reasons for non-intervention), and diagnostic confirmation of pulmonary foci are missing for Case 2. While retrospective limitations are understandable, adding any available clinical context (e.g., whether the patient was deemed unfit for surgery due to systemic instability) will improve completeness.
- **Revision of Section 6 ("Statement regarding illustrations and publication"):** Section 6 (lines 158–163) reads like an internal author drafting note or cover letter declaration rather than formal journal content. This section should be removed from the main narrative and replaced with a standard, formal "Consent for Publication" statement under the Declarations section.
- **Figure Enhancements and Annotations:**
    - In **Figure 1C**, add clear pointer arrows indicating the broad, non-septate hyphae within the necrotic background.

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- Ensure all sub-panel visual labels (A, B, C) are clear and legible across Figures 1, 2, and 3.

5. Discussion and Educational Impact

- **Triggers and Dental Procedures:** Highlight that tooth extraction in a severely neutropenic/aplastic patient serves as a direct mucosal portal of entry for environmental Mucorales spores. Reiterate the vital need for strict oral hygiene protocols, prophylactic coverage, and immediate dental evaluation prior to invasive procedures in hemato-oncology wards.
- **Literature Context:** Briefly contrast the clinical course of mucormycosis in aplastic anemia with other immunosuppressed populations (e.g., post-COVID-19 associated mucormycosis or diabetic ketoacidosis), noting that lack of phagocytic cellular response in AA leads to unchecked angioinvasion.

Final Recommendation

Decision: Accept with Minor Revisions

This manuscript provides valuable clinical lessons on a lethal complication at the intersection of oral-maxillofacial surgery, infectious diseases, and hematology. The presentation of these two fatal cases underscores the fragile equilibrium between aggressive surgical/antifungal therapy and the severe physiological constraints of aplastic anemia. The report is well-conceived, timely, and clinically informative. Once the authors address the minor revisions outlined above—specifically expanding the mycological descriptions, clarifying pharmacological choices, converting Section 6 into standard declaration formatting, and enhancing figure annotations—the manuscript will be well-suited for publication.