Taking a closer look: Clinical and histopathological characteristics of culture-positive versus culture-negative pulmonary mucormycosis

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RESEARCH OBJECTIVE

- Determine if specific clinical or histopathologic characteristics were more likely to predict growth of Mucorales (MCR) in culture
- Determine if specific histological characteristics of MCR portend higher rates of mortality
- Compare histological characteristics of both culture-positive and culture-negative cases of histopathologically documented pulmonary mucormycosis to patient clinical characteristics

BACKGROUND

- Invasive MCR is the second most common invasive mold infection among patients with hematologic malignancies and hematopoietic cell transplant recipients
- Recovery of Mucorales in culture from hypae-laden tissue is poor³
- Detection of MCR in culture from respiratory specimens has been associated with mortality in prior studies¹
- Determinants and clinical implications of culture positivity for MCR is not known

METHODS

- Retrospective review of histology-proven pulmonary mucormycosis cases from April 2000 – April 2021 among patients with hematologic malignancies and hematopoietic cell transplants at the MD Anderson Cancer Center
- 31 patients were identified and screened; 20 cases were included for analysis based on the following criteria:

  **Case Inclusion Criteria**
  - Pulmonary parenchyma
  - Hyphae morphology reported as consistent with MCR
  - Surgical or autopsy specimens (e.g., excisional and core needle biopsies)
  - Fungal culture sent on biopsy specimen & culture positive for MCR or negative for growth
  - Clinical characteristics collected on each patients included: underlying malignancy, transplant history, Diabetes mellitus status, recent antifungal exposure, steroids, and other immunosuppressive medications, malnutrition, renal failure, cytopenia, and survival outcomes
  - Included cases were reviewed by a Thoracic Pathologist (CAM) who was blinded to culture results

  **Case Exclusion Criteria**
  - Case or slide lacking pulmonary parenchyma to evaluate
  - Hyphae morphology suggestive of non-MCR fung
  - Cytology specimens (e.g., FNA, bronchial wash, BAL)
  - Fungal culture sent on biopsy specimen & culture positive for non-MCR fungus

Figures & Images

1. **Figure 1.** Stacked bar chart comparing the distribution of histopathological features of pulmonary MCR in culture-positive vs. culture-negative cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=20)</th>
<th>Culture + (N=15)</th>
<th>Culture - (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46±12</td>
<td>47±12</td>
<td>47±12</td>
</tr>
<tr>
<td>Hematologic Malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>15 (75)</td>
<td>9 (60)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>ALL</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>CLL</td>
<td>1 (5)</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MDS</td>
<td>3 (15)</td>
<td>3 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T-ALL</td>
<td>2 (10)</td>
<td>1 (7)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Monocyteemia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MCR fungal wall invasion</td>
<td>17 (85)</td>
<td>17 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Extensive (&gt;75% of field)</td>
<td>9 (45)</td>
<td>9 (60)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Moderate (50%-75% of field)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Minimal (&lt;50%)</td>
<td>7 (35)</td>
<td>7 (47)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 1. Univariate Analysis of Clinical characteristics in culture-positive vs. culture-negative cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (IQR) [N=6]</th>
<th>Total (N=8)</th>
<th>Culture + (N=5)</th>
<th>Culture - (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>25 (18-30)</td>
<td>25 (18-30)</td>
<td>25 (18-30)</td>
<td>25 (18-30)</td>
</tr>
<tr>
<td>ANC ≤100 cells/µL</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ALC ≤100 cells/µL</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (80)</td>
<td>4 (80)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Steroid use</td>
<td>2 (40)</td>
<td>2 (40)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperglycemia (&gt;200 mg/dL)</td>
<td>3 (60)</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Malnutrition (serum albumin &lt;3 g/dL)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal failure (serum creatinine &gt;2.5 mg/dL)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Results & Conclusions

- Five and 15 patients with histology-proven pulmonary MCR were culture-positive and culture-negative, respectively.
- Univariate analysis of clinical (table 1) and histopathological characteristics (figure 1) did not reveal significant differences between culture-positive and culture-negative cases.
- Histological specimens from culture-positive patients were more likely to exhibit a high burden of necrosis (100% vs. 67% of culture-negative patients, p = 0.19) and to have a high burden of hyphae present (60% vs. 47%, p = 0.60).
- Culture-positive patients were more likely to have acute myeloid leukemia (60% vs. 27%, p = 0.19), history of HCT (80% vs. 53%, p = 0.31), severe lymphopenia (absolute lymphocyte count ≤500/µL, 100% vs. 73%, p = 0.36), and monocytopenia (absolute monocyte count ≤100/µL, 60% vs. 20%, p = 0.11).
- Forty-two patients all-cause mortality of culture-positive (60%) and culture-negative (53%) patients with proven pulmonary MCR was comparable (p = 0.80).

- Our small cohorts lacked the statistical power to identify specific clinical or histopathological characteristics predicting culture positivity in cases of pulmonary MCR.
- Some variables investigated approached significance.
- Future in-depth studies based on multicenter data are needed.

References


HISTOPATHOLOGY

- Each specimen was evaluated on 4 histopathologic features:
  - Amount of fungal hyphae seen on field at 20x objective (Image 1)
  - Degree of tissue invasion seen on field at 10x objective (Image 2)
  - Degree of necrosis seen on field at 10x objective (Image 3)
  - Degree of vascular invasion seen on field at 20x objective (Image 4)
- Each specimen was then graded on amount (% of slide) of each histopathologic feature present (Figure 1):
  - None (0% of field)
  - Scant (<10% of field)
  - Occasional (10%-25% of field)
  - Moderate (>25%-50% of field)
  - Large (>50%-75% of field)
  - Extensive (>75% of field)
- Not available (no structure seen)