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

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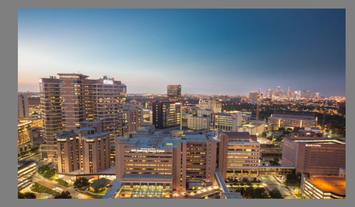

RESEARCH OBJECTIVE

- Determine if specific clinical or histopathologic characteristics were more likely 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 (HCT) recipients[1]
- Recovery of Mucorales in culture from hyphae-laden tissue is poor[2,3]
- Detection of MCR in culture from respiratory specimens has been associated with mortality in prior studies[1]
- Determinants and clinical implications of culture positivity for MCR is not known

METHODS

- Retrospective review of histology-proven pulmonary mucormycosis cases from April 2020 – 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	Case Exclusion Criteria
Pulmonary parenchyma	Case or slide lacking pulmonary parenchyma to evaluate
Hyphae morphology reported as consistent with MCR	Hyphae morphology suggestive of non-MCR fungi
Surgical or autopsy specimens (e.g., excisional and core needle biopsies)	Cytology specimens (e.g., FNA, bronchial wash, BAL)
Fungal culture sent on biopsy specimen & culture positive for MCR or negative for growth	Tissue specimens without a corresponding fungal culture or culture positive for non-MCR fungus

Abbreviations: MCR, Mucor; FNA, fine-needle aspirate; BW, bronchial wash; BAL, bronchioalveolar lavage

- 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

FIGURES & IMAGES

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

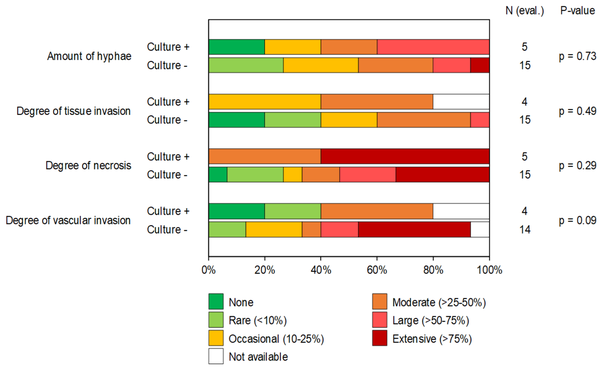

Table 1. Univariate Analysis of Clinical characteristics in culture-positive vs. culture-negative

Characteristics, Median (IQR) or N (%)	Total (N=20)	Culture + (N=5)	Culture – (N=15)	p
Age, years[a]	46.2 (25.5)	43.6 (28.5)	47.1 (27)	-
Hematologic Malignancy				
Leukemia	16 (80)	4 (80)	12 (80)	1
AML	7 (35)	3 (60)	4 (26)	.19
MDS	1 (5)	0 (0)	1 (7)	.94
ALL	5 (25)	0 (0)	5 (33)	.26
CLL	1 (5)	0 (0)	1 (7)	.94
CML	2 (10)	1 (20)	1 (7)	.41
Lymphoma	3 (15)	1 (20)	2 (13)	.72
Multiple Myeloma	1 (5)	0 (0)	1 (7)	.94
HCT	12 (60)	4 (80)	8 (53)	.31
HCT Donor Type				
Allogeneic	11 (55)	4 (80)	7 (46)	.74
Autologous	1 (5)	0 (0)	1 (7)	.74
Acute or chronic GVHD	7 (35)	2 (40)	5 (33)	.79
Risk factors[a]				
Recent antifungal exposure[b]	19 (95)	5 (100)	14 (93)	.75
Steroids[c]	7 (35)	2 (40)	5 (33)	.79
Other immunosuppressive medications	17 (85)	4 (80)	13 (87)	.72
History of Diabetes	7 (35)	1 (20)	6 (40)	.43
Hyperglycemia (>200 mg/dL)	4 (20)	1 (20)	3 (20)	1
Malnutrition (serum albumin ≤3 g/dL)	14 (70)	4 (80)	10 (37)	.58
Renal Failure (serum creatinine >2.5 mg/dL)	1 (5)	0 (0)	1 (7)	.94
Neutropenia[d]	7 (35)	2 (40)	5 (33)	.79
ANC ≤100 cells/uL	6 (30)	2 (40)	4 (26)	.58
Lymphopenia[e]	17 (85)	5 (100)	12 (80)	.48
ALC ≤100 cells/uL	16 (80)	5 (100)	11 (73)	.36
Monocytopenia[f]	6 (30)	3 (60)	3 (20)	.11
Outcomes				
All-cause mortality by 42 days	11 (55)	3 (60)	8 (53)	.80
All-cause mortality by 84 days	13 (65)	4 (80)	9 (60)	.43

Abbreviations. IQR, interquartile range; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease. [a]At time of pulmonary mucormycosis diagnosis; [b] Recent exposures include antifungal prophylaxis and antifungal therapy; [c] Steroid use totaling ≥600 mg prednisone dose equivalent in past 30 days; [d]Absolute neutrophil count ≤500 cells/uL; [e] Absolute lymphocyte count ≤500 cells/uL; [f] Absolute monocyte count ≤100 cells/uL.

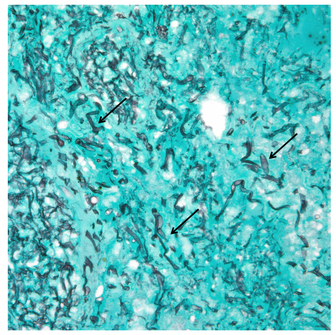

Image 1. GMS staining of a pulmonary tissue highlights broad hyphae (thin arrows) characteristic of MCR (20x objective). Image courtesy of CAM.

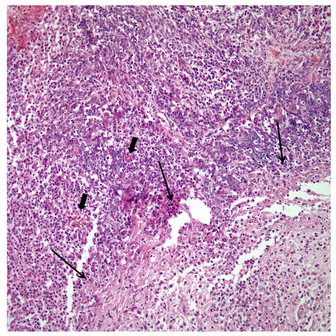

Image 2. H&E staining of lung tissue with caseous necrosis and acute suppurative inflammation (thin arrows) with MCR hyphal element (thick arrows) (10x objective). Image courtesy of CAM.

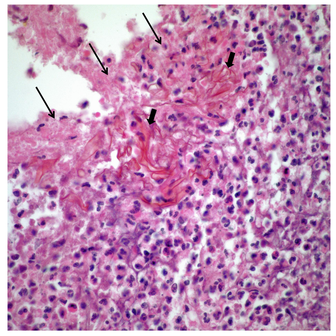

Image 3. H&E staining of a lung tissue with clusters of MCR (thick arrows) embedded in acute inflammation and necrosis (thin arrows) (20x objective). Image courtesy of CAM.

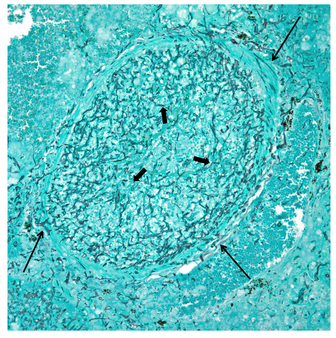

Image 4. GMS staining of characteristic MCR fungal elements inside a blood vessel (thick arrows) with vascular wall invasion (thin arrows) (10x objective). Image courtesy of CAM.

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)

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-day 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

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