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Common co-occurrence in respiratory tract of Mucorales and Gram-negative rods in patients with hematologic malignancy and breakthrough sinopulmonary mucormycosis

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Background/Introduction

Both Mucorales and Gram-negative rods (GNR) commonly infect patients with hematological malignancies (HM); however, the frequency of coinfections with those pathogens is understudied. Prior *in vitro* and *in vivo* laboratory studies show that the simultaneous presence of these pathogens in the same host environment may alter their growth and virulence.[1-6] For example, the iron chelator pyoverdine produced by *Pseudomonas aeruginosa* limits Mucorales growth.[6] Thus, patient outcomes might be influenced by the co-occurrence of these organisms in the same tissue microenvironment.

Objectives

We aimed to A) identify the frequency of Mucorales and GNR sino-pulmonary co-occurrence in patients with hematologic malignancies (HM) and/or stem cell transplant recipients, B) assess differences in clinical variables, such as antibiotic use, across HM patients with and without co-occurrence.

Methods

We retrospectively reviewed the records of 63 consecutive patients with HM malignancies and breakthrough (to mold-active antifungals) sinopulmonary mucormycosis (proven or probable, EORTC/MSG criteria) at MD Anderson Cancer Center (Houston, TX) from 2008-2016. Co-occurrence was defined as a culture positive for GNR taken from either sinus or lung within 90 days (d) of a positive Mucorales culture or histology demonstrating *Mucorales spp*. HM malignancy type and antimicrobial exposures were assessed for associated trends in co-occurrence, including extent of Mucorales disease. We excluded patients with GNR septicemia who had no culture for GNR in respiratory cultures. Immunodeficiency status as classified by neutropenia and/or history of transplant was also assessed

Definitions

[a] Disseminated mucormycosis : defined as Mucorales infection occurring in two non-adjacent anatomical sites

[b] Antibiotics with activity against *Pseudomonas aeruginosa*: ciprofloxacin, levofloxacin, amikacin, meropenem, imipenem, piperacillin-tazobactam, cefepime, ceftazidime

[c] Antibiotics with activity against *Stenotrophomonas*: levofloxacin, minocycline, tigecycline, ceftazidime, trimethoprim-sulfamethoxazole

. Neutropenia was defined as absolute neutrophil count <500 cells/mL.
* - P-value <0.05

Results

	Co-occurrence of Gram-negative rods and Mucorales (n=23) n (%)	Mucorales without co-occurrence of Gram-negative rods (n=40) n (%)
Demographics		
Age (median years with 95% confidence interval)	51	48
Male	15 (65.2)	28 (70.0)
Immunocompromised Status		
Acute myelogenous leukemia	12 (52.2)	22 (55.0)
Acute lymphoblastic leukemia	6 (26.1)	8 (19.5)
Chronic lymphocytic leukemia	4 (17.4)	3 (7.5)
Chronic myelogenous leukemia	1 (4.4)	1 (2.5)
Lymphoma	0.0	5 (12.5)
Multiple myeloma	0.0	1 (2.5)
Neutropenic at time of mucormycosis diagnosis	15 (65.2)	27 (67.5)
History of stem cell transplant	15 (65.2)	25 (62.5)
Involvement of mucormycosis		
Pulmonary	11 (47.8)	22 (53.8)
Nasal/Sinus	13 (56.5)	21 (56.4)
Cerebral	0.0	3 (7.7)
Limited to oral cavity	0.0	2 (2.6)
Disseminated[a]	2 (8.7)	1 (3.9)
Antibiotic Exposures		
Antibiotic(s) with Pseudomonas activity within 14 days of Mucorales cultures [b]	19 (82.6)	39 (97.5)
Antibiotic(s) with Stenotrophomonas activity within 14 days of Mucorales cultures [c]	7 (30.4)	24 (60.0)*
Morbidity & Mortality		
Intubated post-mucormycosis diagnosis	4 (17.4)	15 (37.5)
Expired within 90 days of mucormycosis diagnosis	19 (82.6)	31 (77.5)

Results

- Thirty-eight percent of HM patients demonstrated evidence of GNR and Mucorales co-occurrence within a 90-day window.
- Despite frequent use of antibiotics with activity against *Pseudomonas* (92.1%) and *Stenotrophomonas* (49.2%) within 14 days of Mucorales occurrence, these organisms were commonly isolated within sinopulmonary cultures in a 90-day window.
- Patients without GNR co-occurrence often received at least one agent with activity against *Stenotrophomonas* in the 2 weeks prior to Mucorales diagnosis (P-value = 0.023).
  - This may be indicative of the severity of immunocompromised state (e.g. need for PJP prophylaxis).

  Or
  - Empiric treatment indicative of concern for increased risk of *S. maltophilia* lung infection as Stenotophomonas pneumonia often clinically mimics invasive fungal pneumonia.
- There were no significant differences between the two groups in site, extent of Mucorales infection or crude mortality , which was high (79% within 90d from mucormycosis diagnosis).

Conclusions

Co-isolation of Mucorales and GNR in HM patients is common, with over a third of heavily immunosuppressed pts with breakthrough sinopulmonary mucormycosis harboring GNRs in their respiratory tract.

In a background of high overall mortality, there were no apparent differences in Mucorales infection site, extent of involvement, or survival between patients with and without co-occurring GNR.

Discussion/Future Directions

While it is known that severe immunosuppression predispose to infection by opportunistic molds such as Mucorales and GNRs , the role of metabolic competition (e.g. iron scavenging) or fungal-bacterial metabolites cross-talk may play a mutualistic role in colonization and subsequent invasive infection. Further experimental and clinical studies of the interactions between Mucorales and *P. aeruginosa* or *S. maltophilia* and the role of drugs that act as antifungals or antibacterial siderophores are needed.

References

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