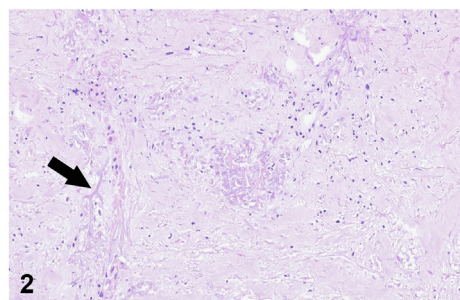


Angioinvasive mucormycosis in a patient with aplastic anemia



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Key words: a; acute; amphotericin; anemia; angioinvasive; angle; aplastic; branching; cutaneous; debridement; frozen; fungal; histology; histopathology; hyphae; in; infection; iron; mucormycete; mucormycetes; mucormycosis; patient; rhizopus; right; section; septate; septation; sequester; sequestration; ulcer; with.



CASE VIGNETTE

A 9-year-old boy with no past medical history was admitted for severe epistaxis and aplastic anemia of unknown etiology with hospital course complicated by bacteremia and the development of a tender plaque on the forearm. Exam revealed a violaceous plaque with peripheral erythema and central necrosis on the left dorsal forearm (Fig 1). Punch biopsies for frozen section and tissue cultures were obtained. Histopathologic exam showed epidermal and dermal necrosis with numerous fungal hyphae in the dermis and within small vessels (Fig 2, black arrow). Tissue fungal culture was positive for *Rhizopus* species.

Question 1: What microscopic fungal morphology is seen?

- A. Septate fungal hyphae branching at right angles
- B. Budding yeasts
- C. Pauci-septated fungal hyphae branching at right angles
- D. Acute angle branching hyphae

E. Pseudohyphae

Answers:

A. Septate fungal hyphae branching at right angles — Incorrect. Septations are not seen in the fungal hyphae here. Septations are “cross walls” that appear at regular intervals throughout the hyphae body. Examples of septated fungi include *Aspergillus*, *Fusarium*, and *Candida* species.

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B. Budding yeasts — Incorrect. There are no budding yeasts visualized. Budding yeasts are characteristic of *Candida* morphology and appear as a small, circular, “budding” outgrowth at the site of cell division.

C. Pauci-septated fungal hyphae branching at right angles — Correct. Mucormycetes are characterized by this morphology. Very rare or no septations are seen and 90 degree angle branching is evident.¹

D. Acute angle branching hyphae — Incorrect. The branching pattern seen is at right angles, not acute. Acute angle branching is seen in hyaline molds including *Aspergillus*, *Fusarium*, and *Scedosporium* species.²

E. Pseudohyphae — Incorrect. No pseudohyphae are seen. Pseudohyphae are characterized by synchronously dividing elongated/ellipsoid yeast cells and are seen in *Candida* species. Pseudohyphae are also always septated, and constrictions are seen at the points of septation.

Question 2: What virulence factor do mucormycotic infections utilize?

- A.** Iron sequestration
- B.** Melanin production
- C.** Polysaccharide capsule
- D.** Thermal dimorphism
- E.** Hydrolytic enzyme secretion

Answers:

A. Iron sequestration — Correct. Mucormycetes sequester iron from their host to support their survival. For this reason, patients with a state of iron overload have an increased incidence and severity of invasive mucormycosis.³

B. Melanin production — Incorrect. The ability to synthesize melanin serves as an important virulence factor in fungal infectivity, possibly by reducing susceptibility to host defense mechanisms. Melanin production has been observed with *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides posadasii*.

C. Polysaccharide capsule — Incorrect. The polysaccharide capsule of *Cryptococcus neoformans* is its dominant virulence factor and aids in interference with host defense mechanisms such as phagocytosis.

D. Thermal dimorphism — Incorrect. Dimorphism allows fungal organisms to switch their morphology and associated gene expression profile in response to mammalian body temperature which confers a survival advantage. Dimorphic fungal organisms include *Candida* species, *Malessezia*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*.

E. Hydrolytic enzyme secretion — Incorrect. Hydrolytic enzymes (such as proteases) allow nutrient extraction from the immediate environment. This virulence factor has been described in *Candida* species and *Aspergillus fumigatus*.

Question 3: Which treatment modality has been shown to most significantly lower the mortality rate of cutaneous mucormycotic infections?

- A.** Amphotericin B
- B.** Liposomal Amphotericin B
- C.** Azoles (eg, itraconazole, posaconazole)
- D.** Surgical debridement
- E.** Iron chelation therapy (eg, deferoxamine)

Answers:

A. Amphotericin B — Incorrect. Amphotericin B is a first-line agent for the treatment of all mucormycotic infections; however, antifungal coverage alone may be insufficient to control infection given that angioinvasion, thrombosis, and tissue necrosis results in poor penetration of antifungal medications.

B. Liposomal Amphotericin B — Incorrect. Liposomal Amphotericin B has a more favorable side effect profile than its non-liposomal counterpart and has been shown to be more efficacious in retrospective studies. However, antifungal coverage alone may be insufficient to control infection given that angioinvasion, thrombosis, and tissue necrosis results in poor penetration of antifungal medications.

C. Azoles (eg, itraconazole, posaconazole) — Incorrect. While azoles are particularly useful as adjunctive medications to broad spectrum antifungals such as amphotericin B to reduce the chance of resistance, antifungal coverage alone may be insufficient to control infection given that angioinvasion, thrombosis, and tissue necrosis results in poor penetration of antifungal medications.

D. Surgical debridement — Correct. Timely surgical debridement of infected tissue after the initiation of antifungal medications is critical in reducing

morbidity and mortality in mucormycotic infections to obtain source control.

E. Iron chelation therapy (eg, deferoxamine) — Incorrect. While iron chelation has a theoretical benefit to treat mucormycosis given iron sequestration as an important virulence factor of mucormycetes, it has actually been shown to be a risk factor for more severe and invasive infection.

Conflicts of interest

None disclosed.

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