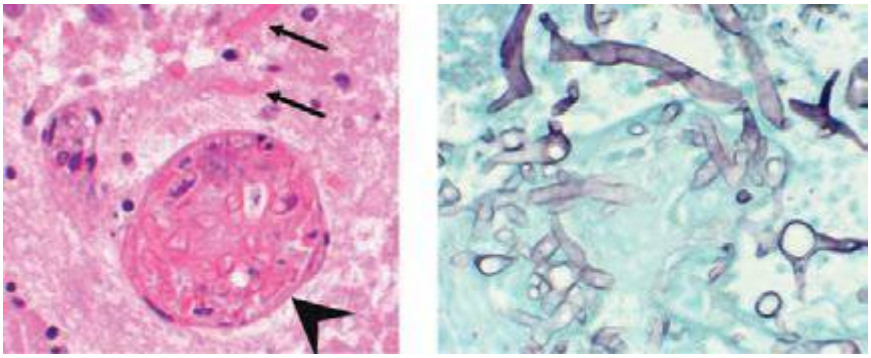
mouth and produce painful necrotic ulcerations of the hard palate, but this is a late finding that suggests extensive, well-established infection.

Pulmonary Disease Pulmonary mucormycosis is the second most common manifestation. Symptoms include dyspnea, cough, and chest pain; fever is often but not invariably present. Angioinvasion results in necrosis, cavitation, and/or hemoptysis. Lobar consolidation, isolated masses, nodular disease, cavities, or wedge-shaped infarcts may be seen on chest radiography. High-resolution chest CT is the best method for determining the extent of pulmonary mucormycosis and may demonstrate evidence of infection before it is seen on chest x-ray. In the setting of cancer, where mucormycosis may be difficult to differentiate from aspergillosis, the presence of ≥10 pulmonary nodules, pleural effusion, or concomitant sinusitis makes mucormycosis more likely. It is critical to distinguish mucormycosis from aspergillosis as rapidly as possible because treatments for these infections differ. Indeed, voriconazole—the first-line treatment for aspergillosis—exacerbates mucormycosis in mouse and fly models of infection.



A ***B***

FIGURE 242-1 Histopathology sections of *Rhizopus oryzae* in infected brain. *A.* Broad, ribbon-like, nonseptate hyphae in the parenchyma (*arrows*) and a thrombosed blood vessel with extensive intravascular hyphae (*arrowhead*) (hematoxylin and eosin). ***B.*** Extensive, broad, ribbon-like hyphae invading the parenchyma (Gomori methenamine silver).

Cutaneous Disease Cutaneous mucormycosis may result from external implantation of the fungus or conversely from hematogenous dissemination. External implantation–related infection has been described in the setting of soil exposure from trauma (e.g., in a motor vehicle accident or natural disaster), penetrating injury with plant material (e.g., a thorn), injections of medications (e.g., insulin), catheter insertion, contamination of surgical dressings, and use of tape to secure endotracheal tubes. Cutaneous disease can be highly invasive, penetrating into muscle, fascia, and even bone. In mucormycosis, necrotizing fasciitis carries a mortality rate approaching 80%. Necrotic cutaneous lesions in the setting of hematogenous dissemination also are associated with an extremely high mortality rate. However, with prompt, aggressive surgical debridement, isolated cutaneous mucormycosis has a favorable prognosis and a low mortality rate.

Gastrointestinal Disease In the past, gastrointestinal mucormycosis occurred primarily in premature neonates in association with disseminated disease and necrotizing enterocolitis. However, there has been a marked increase in case reports describing adults with neutropenia or other immunocompromising conditions. In addition, gastrointestinal disease has been reported as a nosocomial process following administration of medications mixed with contaminated wooden applicator sticks. Nonspecific abdominal pain and distention associated with nausea and vomiting are the most common symptoms. Gastrointestinal bleeding is common, and fungating masses may be seen in the stomach at endoscopy. The disease may progress to visceral perforation, with extremely high mortality rates.

Disseminated and Miscellaneous Forms of Disease Hematogenously disseminated mucormycosis may originate from any primary site of infection. The most common site of dissemination is the brain, but metastatic lesions may also be found in any other organ. The mortality rate associated with dissemination to the brain approaches 100%. Even without central nervous system (CNS) involvement, mortality rates for disseminated mucormycosis exceed 90%. Miscellaneous forms of mucormycosis may affect any body site, including bones, mediastinum, trachea, kidneys, and (in association with dialysis) peritoneum.

DIAGNOSIS

A high index of suspicion is required for diagnosis of mucormycosis. Unfortunately, autopsy series have shown that up to half of cases are diagnosed only post-mortem. Because the Mucorales are environmental isolates, definitive diagnosis requires a positive culture from a sterile site (e.g., a needle aspirate, a tissue biopsy specimen, or pleural fluid) or histopathologic evidence of invasive mucormycosis. A probable diagnosis of mucormycosis can be established by culture from a nonsterile site (e.g., sputum or bronchoalveolar lavage) when a patient has appropriate risk factors as well as clinical and radiographic evidence of disease. However, given the urgency of administering therapy early, the patient should be treated while confirmation of the diagnosis is awaited.

Biopsy with histopathologic examination remains the most sensitive and specific modality for definitive diagnosis (Fig. 242-1). Biopsy reveals characteristic wide (≥6- to 30-μm), thick-walled, ribbon-like, aseptate hyphal elements that branch at right angles. Other fungi, including *Aspergillus*, *Fusarium*, and *Scedosporium* species, have septa, are thinner, and branch at acute angles. Because artificial septa may result from folding of tissue during processing (which may also alter the appearance of the angle of branching), the width and the ribbon-like form of the fungus are the most reliable features distinguishing mucormycosis. The Mucorales are visualized most effectively with periodic acid–Schiff or methenamine silver stain or, if the organism burden is high, with hematoxylin and eosin. While histopathology can identify the Mucorales, specific species can be identified only by culture. Polymerase chain reaction (PCR) is being investigated as a diagnostic tool for mucormycosis but is not yet approved by the U.S. Food and Drug Administration (FDA) for this purpose and is not generally available.

Unfortunately, cultures are positive in fewer than half of cases of mucormycosis. Nevertheless, the Mucorales are not fastidious organisms and tend to grow quickly (i.e., within 48 h) on culture media. The likely explanation for the low sensitivity of culture is that the Mucorales form long filamentous structures that are killed by tissue homogenization—the standard method for preparing tissue cultures in the clinical microbiology laboratory. Thus the laboratory should be advised when a diagnosis of mucormycosis is suspected, and the tissue should be cut into sections and placed in the center of culture dishes rather than homogenized. There is also substantial variability among isolates in optimal growth temperature, so growth at both room temperature and 37°C is advisable.

Imaging techniques often yield subtle findings that underestimate the extent of disease. For example, the most common finding on CT or MRI of the head or sinuses of a patient with rhino-orbital mucormycosis is sinusitis that is indistinguishable from bacterial sinusitis. It is also common to detect no abnormalities in sinus bones despite clinical evidence of progressive disease. MRI is more sensitive (~80%) for detecting orbital and CNS disease than is CT. High-risk patients should always undergo endoscopy and/or surgical exploration, with biopsy of the areas of suspected infection. If mucormycosis is suspected, initial empirical therapy with a polyene antifungal agent should be initiated while the diagnosis is being confirmed.

DIFFERENTIAL DIAGNOSIS

Other mold infections, including aspergillosis, scedosporiosis, fusariosis, and infections caused by the dematiaceous fungi (brown-pigmented