Pulmonary Mucormycosis: Risk Factors, Radiologic Findings, and Pathologic Correlation

Rishi Agrawal, MD
Anjana Yeldandi, MD
Hatice Savas, MD
Nishant D. Parekh, MD
Pamela J. Lombardi, MD
Eric M. Hart, MD

Abbreviations: IPA = invasive pulmonary aspergillosis, PM = pulmonary mucormycosis

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From the Departments of Radiology (R.A., H.S., N.D.P., P.J.L., E.M.H.) and Pathology (A.Y.), Northwestern University Feinberg School of Medicine, 676 N St. Clair St, Ste 800, Chicago, IL 60611. Presented as an education exhibit at the 2018 RSNA Annual Meeting. Received May 13, 2019; revision requested August 15 and received September 9; accepted September 24. For this journal-based SA-CME activity, the author N.D.P. has provided disclosures (see end of article); all other authors, the editor, and the reviewers have disclosed no relevant relationships. **Address correspondence to** R.A. (e-mail: *ragrawal@nm.org*).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- List the risk factors for PM.
- Identify specific and nonspecific imaging signs of PM.
- Describe the treatment of PM.

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Pulmonary mucormycosis (PM) is an uncommon fungal infection most often seen in immunocompromised patients. The fungus grows on decaying food, soil, and animal excrement. Patients usually become infected by inhalation of spores. The most common risk factors include diabetes mellitus, hematologic malignancy, and solid organ or stem cell transplant. PM can have a nonspecific appearance at imaging. For example, early imaging may show peribronchial ground-glass opacity. Later, the disease progresses to consolidation, nodules, or masses. Because patients are usually immunocompromised, the differential diagnosis often includes invasive pulmonary aspergillosis (IPA). Various radiologic findings suggestive of PM have been identified to help differentiate it from IPA. For example, the reverse halo sign is more closely associated with PM than with IPA. The reverse halo sign is an area of ground-glass opacity surrounded by a rim of consolidation. In addition, the presence of pleural effusions and more than 10 nodules is more suggestive of PM than it is of IPA. PM can progress rapidly in neutropenic patients. Identification of the hyphae in tissue by using endobronchial or percutaneous sampling can allow differentiation from IPA and help confirm the diagnosis of mucormycosis. Because of the high mortality rate associated with PM, early identification of the disease is critical for an improved likelihood of survival. A multimodality treatment approach with antifungal agents and surgical débridement has been shown to improve outcomes. The authors review the risk factors for PM, describe its imaging appearance and disease process, and describe the treatment of the disease.

Introduction

Mucormycosis represents a group of fungal infections caused by members of the order Mucorales that can involve many different organs, including the skin, paranasal sinuses, orbits, brain, lungs, and gastrointestinal tract. We focus on the risk factors and radiologic appearance of pulmonary mucormycosis (PM). Although PM is relatively uncommon compared with other fungal infections of the lung, knowledge of its radiologic appearance and evolution is important because of the high morbidity and mortality rates in infected patients. The imaging findings can be nonspecific, but there are some specific radiologic clues that can aid diagnosis. Because early treatment with antifungal agents improves survival, the radiologist can play a key role in treatment of the patient (1).

TEACHING POINTS

- The risk factors for mucormycosis include uncontrolled diabetes mellitus, hematologic malignancy (acute leukemia in particular), stem cell transplant, solid organ transplant, neutropenia, deferoxamine therapy, and corticosteroid use.
- In early PM, initial CT may simply show a perivascular ground-glass lesion prior to the development of more extensive imaging findings. Ground-glass lesions usually progress to consolidation, nodules, or masses.
- Clinical clues that suggest PM rather than IPA include concurrent sinus infection (odds ratio [OR], 25.7 [95% confidence interval (CI): 1.47, 448.15]) and previous voriconazole therapy (OR, 7.8 [95% CI: 1.32, 45.53]). Imaging findings that are more suggestive of PM than IPA include the presence of more than 10 lesions (OR, 19.82 [95% CI: 1.94, 202.29]) and the presence of pleural effusion (OR 5.1 [95% CI: 1.06, 24.23]).
- While most fungal pneumonia shows nonspecific signs at imaging, the reverse halo sign has been shown to be a specific sign of mucormycosis, occurring in 19%–94% of patients with PM.
- At histologic examination, one of the hallmarks of PM is hyphal invasion of large and small blood vessels, resulting in thrombosis and infarction.

Taxonomy and Life Cycle

The term *zygomycosis* encompasses agents that cause mucormycosis and entomophthoramycosis, but the term has been discarded in the modern taxonomy literature. The previous taxonomy had been based on similarities in the structure, life cycle, and ecology of the fungi. However, more recent analysis of the molecular biology has separated the two into different subphyla (2). In addition, entomophthoramycosis is clinically different from mucormycosis. Unlike mucormycosis, entomophthoramycosis is most commonly found in tropical climates, affects immunocompetent patients, and causes a chronic infection (3). For these reasons, the more specific terms mucormycosis, *Mucor* infection, or simply *Mucor* are preferred over zygomycosis. Most cases of mucormycosis are caused by members of the genus *Rhizopus* or *Mucor*. However, there are many other genera in the order Mucorales that can cause infections in humans (Fig 1) (4).

The fungi that cause mucormycosis are commonly found on decaying food, soil, and animal excrement (Fig 2a) (4). A spore from the environment divides and forms ribbonlike hyphae on the substrate. In asexual reproduction, an upright stalk called a sporangiophore grows from the hyphae (Fig 2c, 2d) (3). The tip of the sporangiophore differentiates into a rounded sac called a sporangium from which new spores develop (3). Sinus and lung infection occur by inhalation and deposition of the spores in these tissues (Fig 2b). Cutaneous infection can occur when there is disruption of the skin in the case of burns or trauma (4).

		Frequency of infection
Kingdom	Fungi	
Subphylum	Mucoromycotina	
Order	Mucorales	
Family	Mucoraceae	
Genera	Rhizopus	47%
	Mucor	18%
	Cunninghamella	7%
	Apophysomyces	5%
	Lichtheimia	5%
	Saksenaea	5%
	Rhizomucor	4%

Figure 1. Taxonomic hierarchy of the genera that most commonly cause mucormycosis.

Risk Factors and Epidemiology

Mucormycosis can involve many different organs. The most common site of infection is rhinocerebral, followed by cutaneous, lung, disseminated, and gastrointestinal tract (5). The risk factors for mucormycosis include uncontrolled diabetes mellitus, hematologic malignancy (acute leukemia in particular), stem cell transplant, solid organ transplant, neutropenia, deferoxamine therapy, and corticosteroid use (5).

Some risk factors are more closely associated with specific sites of involvement. For example, solid organ transplant is more uniquely associated with lung infection, whereas diabetes mellitus is more closely associated with the rhinocerebral form (4). Because growth of the fungi is stimulated by a high blood glucose concentration, infection is rare in patients with well-controlled blood glucose levels.

A systematic review of the literature published between 2000 and 2017 examining a total of 851 patients with all forms of mucormycosis revealed geographic differences in the risk factors (5). Worldwide, diabetes mellitus was the most common risk factor (occurring in 40% of patients), but it was particularly more common in Asia (46%) and Africa (75%) compared with in Western countries (36%). Hematologic malignancy was the next most common risk factor (32%), followed by solid organ transplant (14%). Notably, in 18% of patients with all types of mucormycosis, no predisposing condition was identified (5).

Intrapulmonary Imaging Manifestations

Nonspecific Signs

The appearance of PM at imaging is varied. At chest radiography, lobar and segmental consolidation is the most common imaging finding, and

Figure 2. Structure of *Mucor*. **(a)** Macroscopic photograph shows *Mucor* sporangia growing on old bread. (Photograph used under license from Rattiya Thongdumhyu/Shutterstock.com). **(b)** Photomicrograph of a fungus ball obtained from lung tissue shows multiple clustered hyphae and sporangia. (Original magnification, ×100.) **(c)** High-power photomicrograph shows a spherical structure called the sporangium. (Lactophenol cotton blue stain.) The wall of the sporangium dissolves on maturity, exposing the spores. **(d)** Drawing of a sporangium at the tip of a hyphal stalk. (Drawing used under license from Kallayanee Naloka/Shutterstock.com.)

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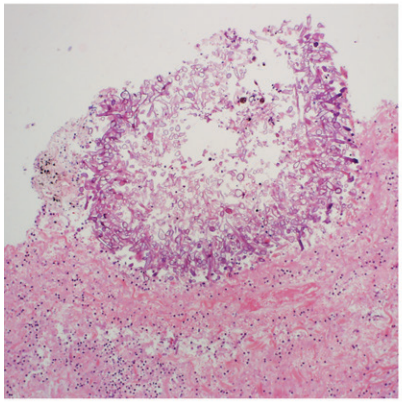

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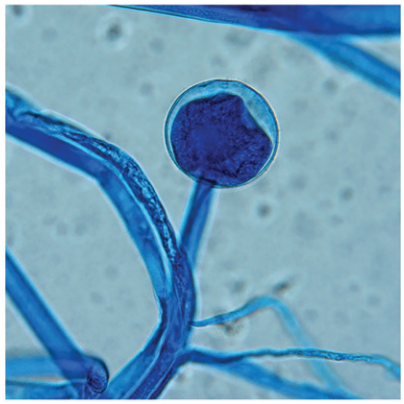

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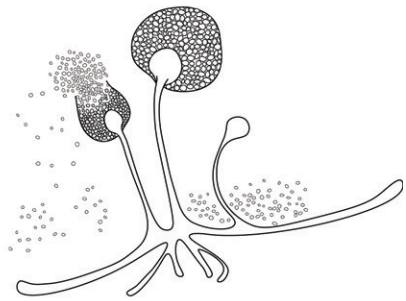


d.

imaging in some patients shows a multilobar distribution (6). Unilateral infection can progress quickly to the contralateral lung if left untreated (Fig 3). A multifocal pneumonia pattern with bilateral consolidation has a high correlation with increased mortality (7). Single or multiple nodules and masses are also common features (6).

CT features of infection are similarly variable. In early PM, initial CT may simply show a perivascular ground-glass lesion prior to the development of more extensive imaging findings (7). Ground-glass lesions usually progress to consolidation, nodules, or masses (Figs 3, 4). Nodules and masses may have a ground-glass halo, but this is a nonspecific sign with a reported frequency between 19% and 53% (7–9). In addition, because it is commonly described as an imaging feature of invasive pulmonary aspergillosis (IPA), a ground-glass halo is less useful as a diagnostic aid (Fig 5).

Because the fungus tends to invade the vasculature, necrosis is a common feature (Fig 6). Consolidation and masses may show a relative paucity of air bronchograms at imaging (7), a finding also seen in patients with bland pulmonary infarction. Occasionally, a cavity can appear at imaging as the initial manifestation (Fig 7). Other vascular findings that have been described include pseudoaneurysm formation and abrupt termination of a pulmonary artery branch, which appears with the vascular cutoff sign (7).

Infection can spread to the pleura, chest wall, mediastinum, diaphragm, and heart (10). Pleural thickening or effusion may indicate pleural infection. Air in the intercostal space or subcutaneous soft tissues usually indicates chest wall spread (Fig 7).

Rarely, patients may present with an invasive endobronchial or endotracheal mass (Fig 8). These lesions have been described in patients with diabetes mellitus and manifest with a less fulminant course. However, because of the central location, the lesions can invade the central vasculature and cause fatal hemoptysis (4).

One of the diagnostic challenges in patients suspected of having invasive fungal pneumonia is differentiating aspergillosis from mucormycosis. Chamilos et al (11) studied 45 patients with IPA or PM. According to their findings, clinical clues that suggest PM rather than IPA include concurrent sinus infection (odds ratio [OR], 25.7 [95% confidence interval (CI): 1.47, 448.15]) and previous voriconazole therapy (OR, 7.8 [95% CI: 1.32, 45.53]). Imaging findings that are more suggestive of PM than IPA include the presence of more than 10 lesions (OR, 19.82 [95% CI: 1.94, 202.29]) and the presence of pleural effusion (OR 5.1 [95% CI: 1.06, 24.23]) (11).

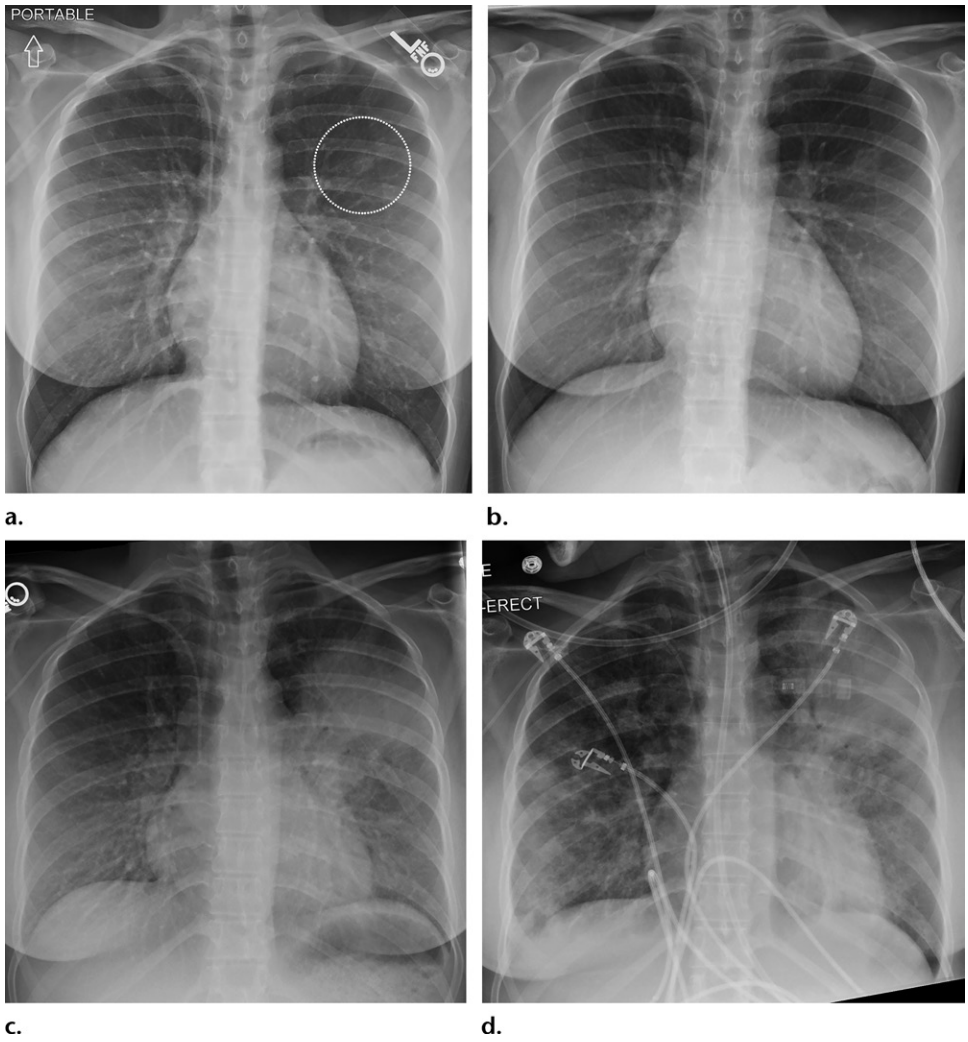


Figure 3. Unilateral PM progressing to infection of the contralateral lung in a 35-year-old-woman who recently underwent stem cell transplant for multiple myeloma. **(a)** Frontal radiograph shows a nodular opacity (dotted circle) in the left upper lung. **(b)** Frontal radiograph obtained on day 2 shows enlargement of the nodular opacity. **(c)** Frontal radiograph obtained on day 4 shows marked enlargement of the left upper lobe lesion with a masslike consolidation. **(d)** Frontal radiograph obtained on day 7 shows progressive consolidation in the left upper lobe and new airspace disease in the right lung. The patient died 2 days later.

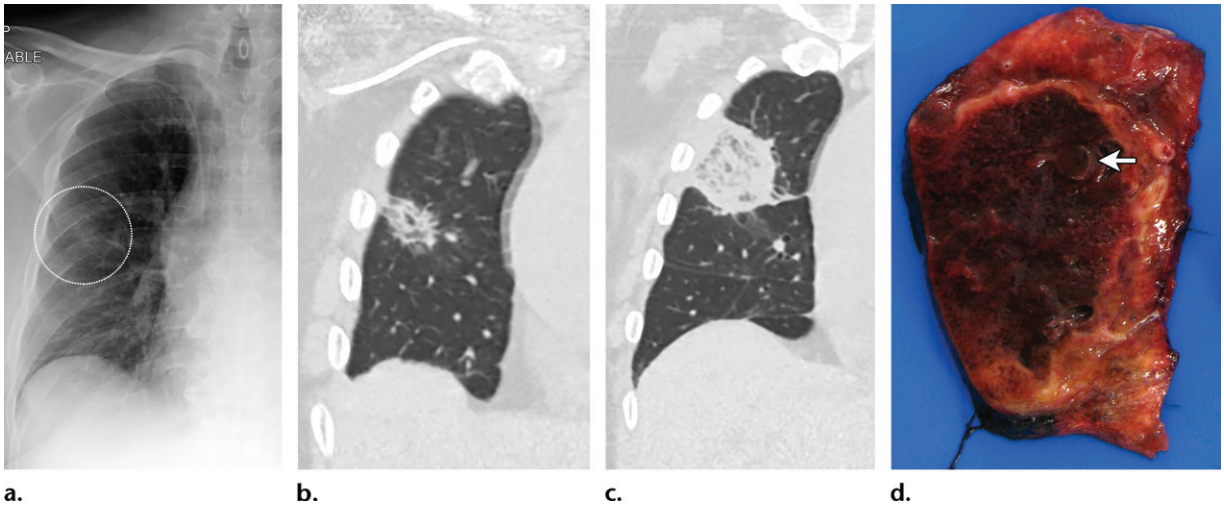
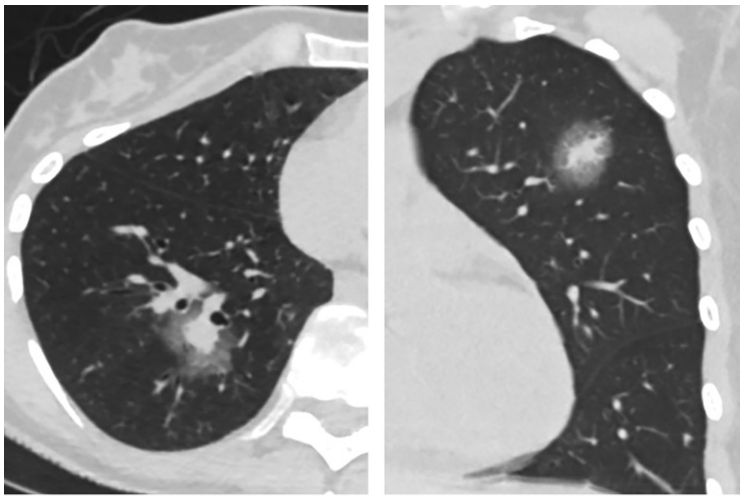
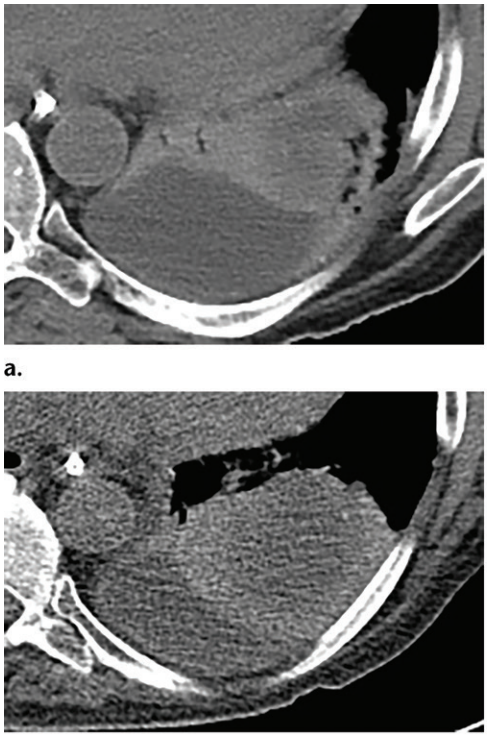


Figure 4. Ground-glass opacity progressing to an enlarged lesion in a 66-year-old man who underwent recent stem cell transplant for aplastic anemia. **(a)** Frontal radiograph of the right lung shows a faint area of ground-glass opacity (dotted circle) in the right midlung. **(b)** Coronal CT image obtained on day 2 shows an area of nodular ground-glass opacity. **(c)** Coronal CT image obtained on day 12 shows enlargement of the lesion with development of the reverse halo sign. **(d)** Lobectomy specimen shows an area of necrosis with a thick wall. Note the thrombosed vessel (arrow).



a. b.

Figure 5. CT halo sign. Axial CT image in a patient with IPA **(a)** and coronal CT image in a patient with PM **(b)** depict a central solid nodule surrounded by an area of ground-glass opacity.



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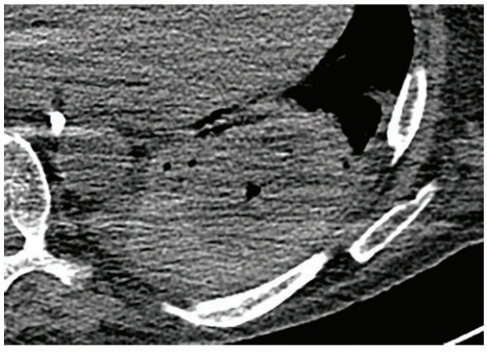

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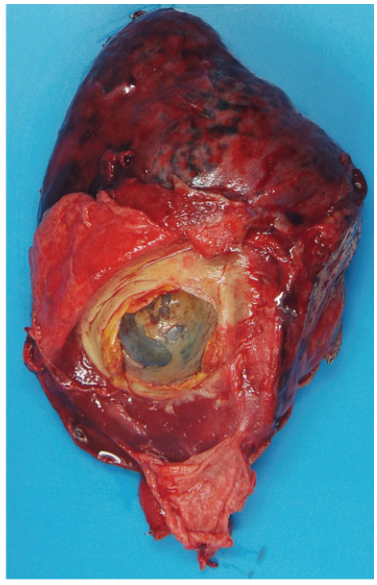


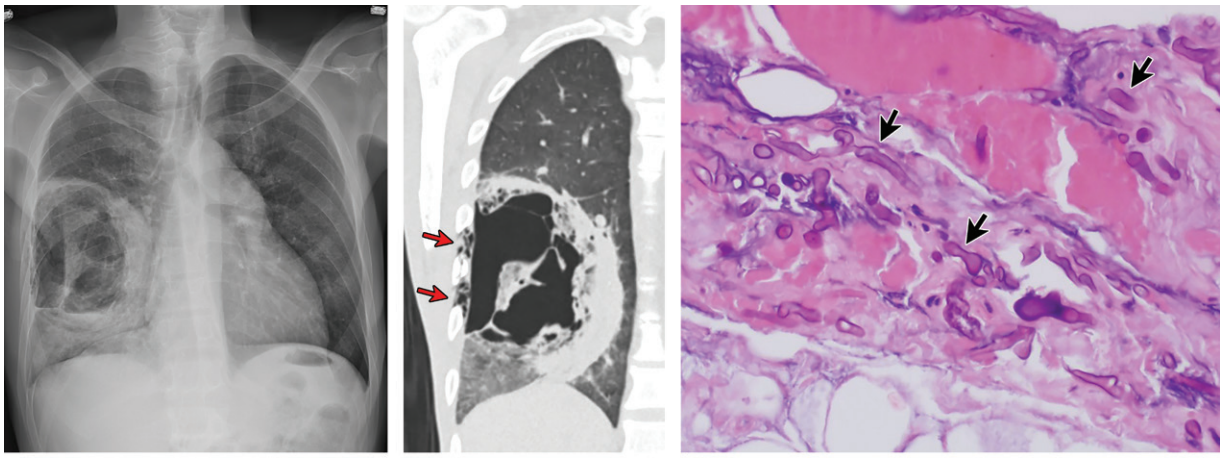
d.

Figure 6. Necrosis in a 59-year-old man who underwent renal transplant. **(a)** Axial CT image demonstrates a necrotic consolidation in the left lower lobe with adjacent pleural effusion. **(b)** Axial CT image depicts enlargement of the consolidation after 20 days with new pleural thickening. **(c)** Axial CT image shows central cavitation in the left lower lobe lesion. **(d)** Gross photograph shows the left lung with the necrotic cavity exposed.

Reverse Halo Sign

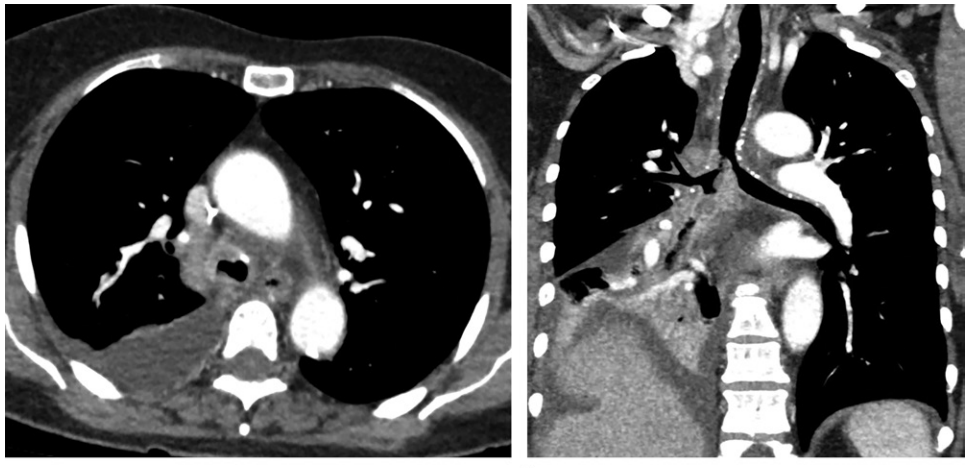
The reverse halo sign is defined as a ground-glass lesion with a peripheral rim of consolidation (Figs 4c, 9, 10). While most fungal pneumonia shows nonspecific signs at imaging, the reverse halo sign has been shown to be a specific sign of mucormycosis, occurring in 19%–94% of patients with PM (Table) (7–9,12,13). The wide range in the reported frequency of the reverse halo sign is likely due to the severity of the underlying disease and the presence of neutropenia at diagnosis.

For example, in a study by Legouge et al (13), 752 patients with acute leukemia were evaluated. Sixteen patients were found to have PM, and the reverse halo sign was depicted at initial imaging in all patients but one. The one patient in whom imaging did not show the reverse halo sign was not neutropenic at the time of diagnosis. Another study of 27 patients with PM showed that the



a. b. c.

Figure 7. Chest wall spread of PM in a 44-year-old man who underwent renal transplant. **(a)** Frontal radiograph shows a large cavity with an air-fluid level in the right lower lung. There is subcutaneous emphysema in the adjacent right chest wall. **(b)** Coronal CT image shows right lower lobe consolidation and air (arrows) in the adjacent intercostal spaces. **(c)** Photomicrograph of a biopsy specimen shows Mucorales hyphae (arrows) interspersed in muscle tissue. (Original magnification, ×400.)



a. b.

Figure 8. Endobronchial mucormycosis. **(a)** Axial CT image shows soft-tissue thickening of the lateral and anterior trachea with ill definition of the surrounding fat. **(b)** Coronal multiplanar curved reconstruction from CT of the tracheobronchial tree shows extensive soft tissue in and around the carina and right main bronchi ,with occlusion of the bronchus intermedius and right lower lobe collapse. (Case courtesy of Cameron Hassani, MD, University of California, Los Angeles, Los Angeles, Calif.).

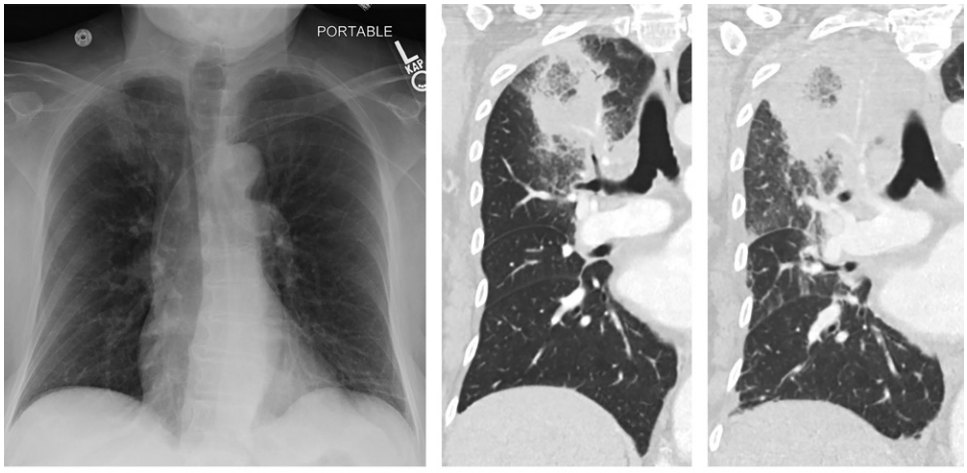
reverse halo sign is more common in patients with neutropenia compared with in those without neutropenia (79% versus 31%) (9).

The reverse halo sign can also help distinguish between other fungal pneumonias, particularly IPA. In a study of 189 patients with fungal pneumonia and 32 with PM, Wahba H et al (12) found eight patients in whom CT depicted a reverse halo sign. Seven of the eight patients had PM, and one patient had IPA. In another review of 24 patients with PM and 96 patients with IPA, the reverse halo sign was found in 54% of patients with PM, compared with only 6% of those with IPA (8).

Nam et al (14) showed a characteristic progression of CT findings in 15 patients with PM. In that imaging series, nodules, masses, or consolidation appearing with a CT halo sign progressed to a reverse halo sign, followed by central necrosis, and finally, an air crescent sign. This progression was associated with a tendency toward a gradual increase in the neutrophil count, although this association was not statistically significant (14).

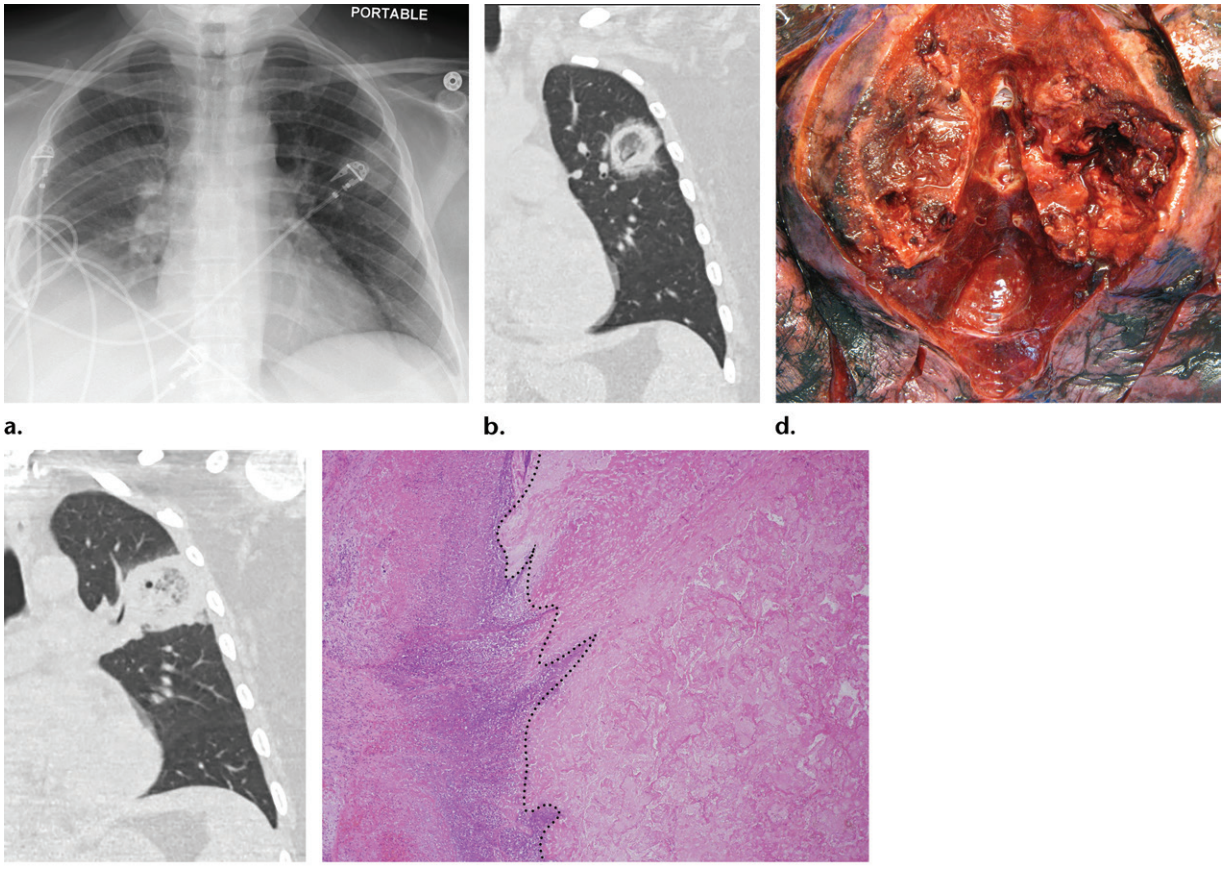
The reverse halo sign can represent other processes in different contexts. The differential diagnosis includes organizing pneumonia, bland pulmonary infarct, and lung cancer. The clinical context should help differentiate these entities. Most patients with PM have some form of immunodeficiency. In addition, mucormycosis shows relatively rapid progression at serial chest radiography compared with these other entities (Fig 11).

Figure 9. PM appearing with the reverse halo sign in a 68-year-old woman with acute myeloid leukemia. **(a)** Frontal radiograph shows a right upper lobe consolidation. **(b)** Coronal CT image obtained 1 day later shows a right upper lobe consolidation with an area of central ground-glass opacity (reverse halo sign). **(c)** Coronal CT image obtained on day 5 shows progressive consolidation occupying greater than half of the right upper lobe.



a. b. c.

Figure 10. PM appearing with the reverse halo sign in a 35-year-old man with multiple myeloma. **(a)** Frontal radiograph shows a nodular consolidation in the left upper lobe. **(b)** Coronal CT image obtained on the same day shows a lesion with a reverse halo sign. **(c)** Coronal CT image obtained 7 days later shows enlargement of the lesion. **(d)** Cut surface of the lobectomy specimen shows a cavitary mass with central necrosis and hemorrhage. **(e)** Photomicrograph of the lesion margin shows an area of necrosis (right of dotted line) with a zone of transition (left of dotted line) containing inflammatory cells and variable fibrosis. (Original magnification, ×40.)



a. b. d.

c. e.

Reverse Halo Sign in Patients with PM

Study*	No. of Patients in Study	No. of Patients with Reverse Halo Sign†
Hammer et al (7)	30	18 (60)
Jung et al (8)	24	13 (54)
Bourcier et al (9)	27	15 (55)
Wahba et al (12)	37	7 (19)
Legouge et al (13)	16	15 (94)
Nam et al (14)	20	7 (35)

*Note.—Numbers in parentheses are references.
†Note.—Numbers in parentheses are percentages.

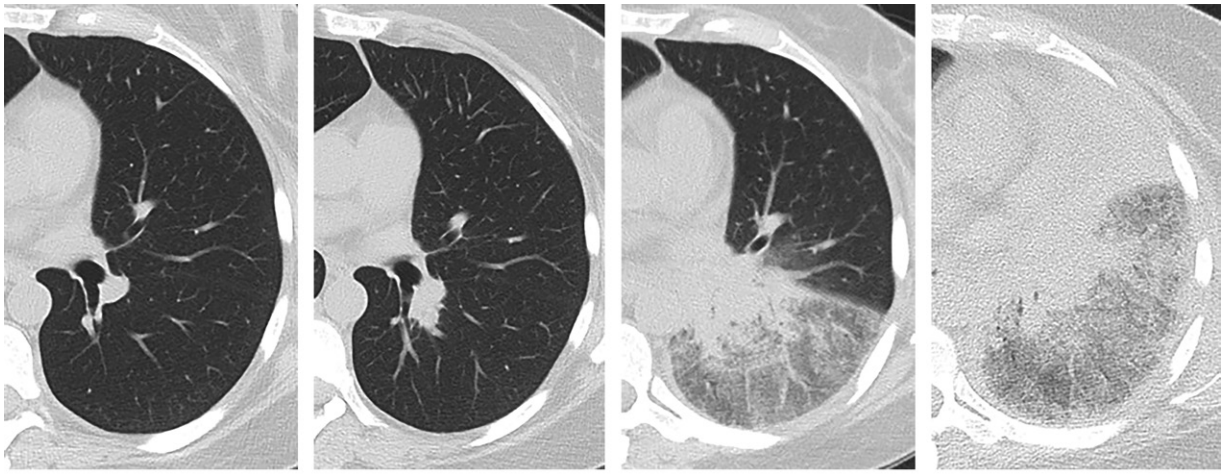


Figure 11. Rapid progression of PM in a 41-year-old woman who underwent stem cell transplant for acute myeloid leukemia. **(a)** Axial CT image of the left lung is clear on day 1. Note the patent superior segmental left lower lobe bronchus. **(b)** Axial CT image obtained on day 12 shows a new nodule in the left lower lobe abutting the superior segmental bronchus. **(c)** Axial CT image obtained on day 21 shows increased consolidation and complete lobar ground-glass opacification. The superior segmental bronchus is now occluded. **(d)** Axial CT image obtained on day 23 shows left upper lobe collapse and continued complete ground-glass opacification of the left lower lobe.

Biopsy

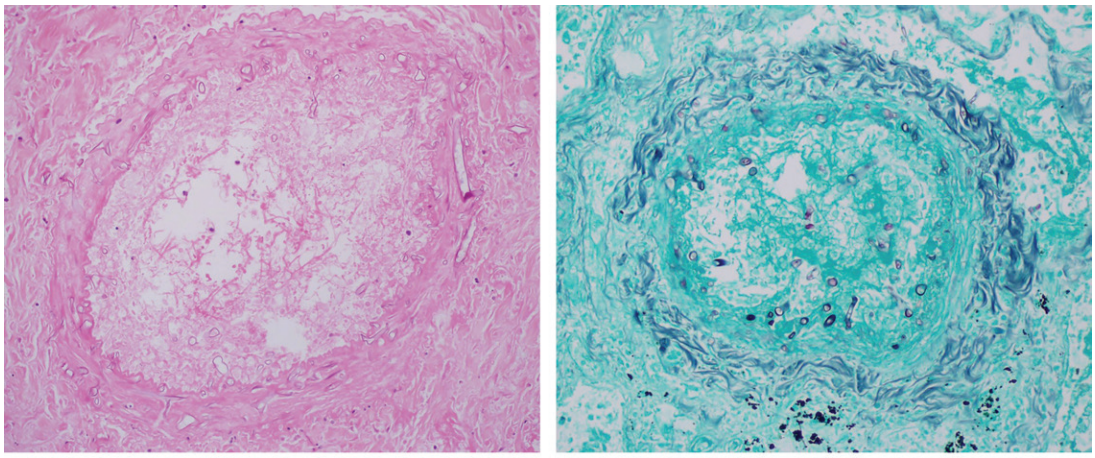
Both bronchoscopic and percutaneous lung biopsy are effective tools to help diagnose PM. In a study of 61 patients who underwent CT-guided lung biopsy for CT findings suspicious for fungal pneumonia, laboratory testing results in 80% of patients were shown to be positive for fungal infection by using Calcofluor white staining. Thirteen (27%) of these were shown to have mucormycosis. In the remaining 12 patients with negative test results for fungal infection, nine had an alternative diagnosis, including lung cancer, leukemic infiltrate, or tuberculosis (15).

Although the process is not widely available, demonstrating circulating Mucorales DNA by using quantitative polymerase chain reaction (qPCR) has been shown to be an effective method for revealing mucormycosis in patients with cutaneous, rhinocerebral, pulmonary, and disseminated forms. In one series of 10 patients with mucormycosis, qPCR showed circulating Mucorales DNA in nine patients between 68 and 3 days before a formal diagnosis was made on the basis of the results of histopathologic testing or culture (16). In another study of patients with cutaneous disease, qPCR demonstrated Mucorales DNA 11 days before the formal diagnosis (17).

Disease Characteristics

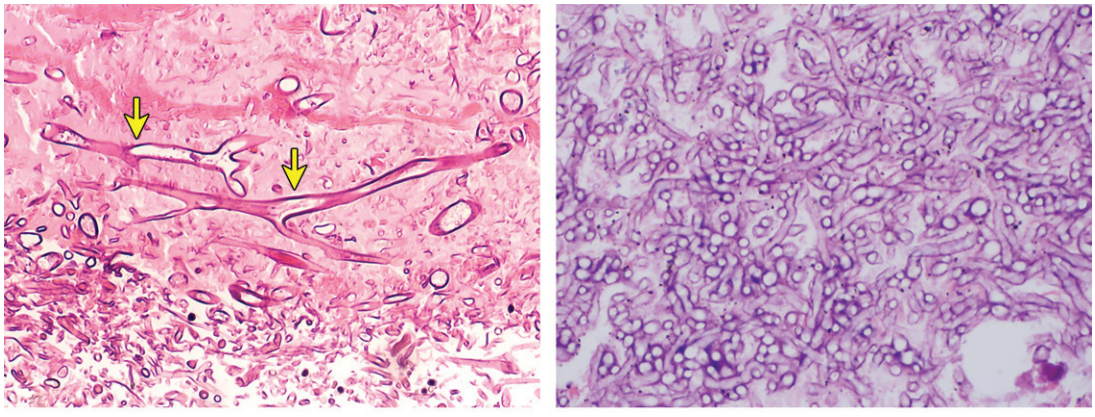
Gross examination of infected lung tissue can show variable features. Lesions can be firm, hyperemic, hemorrhagic, or necrotic. When infarction is present, central lesions tend to be round compared with peripheral lesions, which are usually wedge shaped (10). Direct invasion of adjacent tissues may be present, including the chest wall, mediastinum, diaphragm, and heart (10).

At histologic examination, one of the hallmarks of PM is hyphal invasion of large and small blood vessels, resulting in thrombosis and infarction (Figs 4d, 12). Staining with phosphotungstic acid hematoxylin can show fine threads of fibrin on the



a. b.

Figure 12. Cross sections through blood vessels in the lung parenchyma. Photomicrographs enhanced with hematoxylin-eosin stain (original magnification, ×200) **(a)** and Gomori methenamine silver stain (original magnification, ×200) **(b)** show invasion of the vessels by hyphae. Vessel invasion is accompanied by surrounding tissue edema and necrosis.



a. b.

Figure 13. Differentiation of *Mucor* and *Aspergillus* at histologic examination. **(a)** Photomicrograph of *Mucor* hyphae shows broad ribbonlike hyphae (arrows) that are 7–15 μm wide. (Hematoxylin-eosin stain; original magnification, ×600.) The hyphae lack regular septa and are pauciseptate. The hyphae have irregular wide-angle branches. (Image used under license from David Litman/Shutterstock). **(b)** Photomicrograph of *Aspergillus* hyphae shows thin uniform hyphae with regular septa. (Hematoxylin-eosin stain; original magnification, ×600.) The hyphae have regular acute-angle branching and have uniform walls.

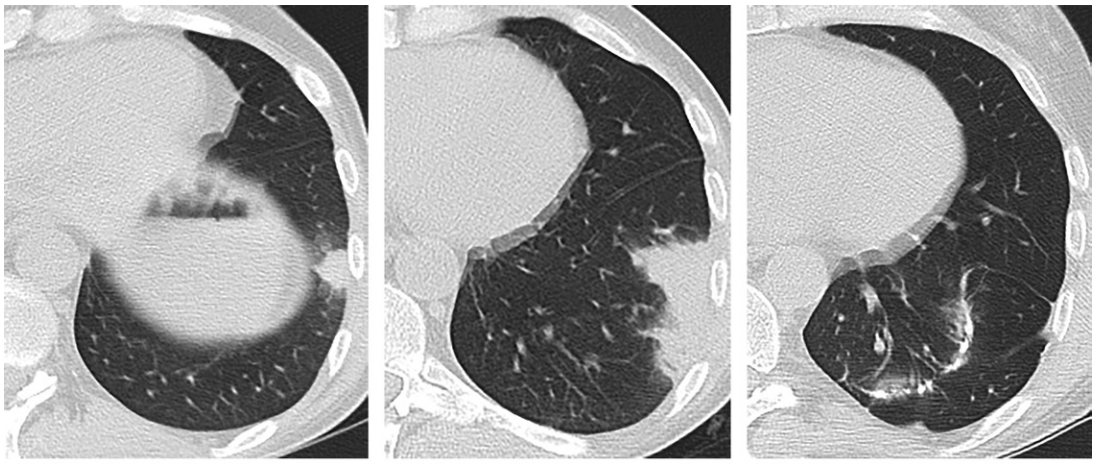
hyphal surfaces in blood vessels, indicating thrombogenic activity (18). Lesions have a variable level of neutrophilic infiltration depending on the degree of neutropenia. Other infections may coexist in the specimen, particularly in immunocompromised hosts, including *Aspergillus*, *Candida*, bacterial, viral, and protozoal infection (18). At histologic examination in patients with a reverse halo sign, there is central necrosis with a peripheral zone of transition containing inflammatory cells, variable fibrosis, and fungal hyphae (Fig 10e).

Experienced practitioners can distinguish mucormycosis from the *Aspergillus* species at histologic examination. Unlike in *Aspergillus*, hyphae in mucormycosis are broad (7–15 μm) with few—if any—septa (Fig 13) (10). False septa may occur in the specimen because of shrinkage from processing. *Mucor* hyphae have been described as ribbonlike (18). Hyphae have irregular wide branches, compared with the regular acute-angle branching in *Aspergillus* species (10).

Treatment

If feasible, attempts to reverse the underlying predisposing factors for infection should be made. Treatment may include control of blood glucose levels, treatment of metabolic acidosis, or tapering of immunosuppressive agents (19). Treatment then consists of antifungal therapy and, if possible, surgical débridement of affected tissue.

Prompt initiation of appropriate therapy is critical for patients with PM. In a study of 70 patients, the majority with PM or disseminated disease, a delay in the initiation of amphotericin



a. b. c.

Figure 14. Surgical treatment of PM in a 51-year-old man with renal and stem cell transplants complicated by graft-versus-host disease. **(a)** Axial CT image of the left lower lobe shows a nodule with mild surrounding ground-glass opacity. **(b)** Axial CT image obtained 1 month later depicts an enlarged nodule. **(c)** Axial CT image obtained at follow-up 5 months after surgery shows complete resolution with no recurrence.

B–based therapy was associated with a twofold increase in mortality (1). Lipid formulations of amphotericin B are associated with less renal impairment compared with conventional amphotericin B deoxycholate.

Most azole antifungal agents have no significant activity against mucormycosis (4). These agents include fluconazole and voriconazole, which are commonly used as antifungal prophylaxis or for treatment of *Candida* and *Aspergillus* infection. Posaconazole is a newer broad-spectrum triazole that has shown activity against many species of the order Mucorales (4). However, posaconazole is not currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of mucormycosis, although open-label studies evaluating its use as a salvage therapy for PM have shown a success rate between 65% and 70% (20). Isavuconazole is another newer broad-spectrum triazole. It is FDA approved for primary and salvage treatment of mucormycosis, although data comparing its effectiveness with that of amphotericin B are limited (21).

Surgery is recommended for patients with localized disease and results in improved outcomes compared with in those treated with antifungal therapy alone (21,22). Surgery is usually reserved for patients with unifocal disease and can consist of wedge resection, lobectomy, or pneumonectomy (Fig 14). Surgery for bilateral disease is uncommon but has been shown to be effective for source control (23).

Conclusion

PM has a high mortality rate, in part because of the underlying risk factors for the disease. The most common risk factors include diabetes mellitus, hematologic malignancy, and solid organ and stem cell transplant. Early imaging findings may be nonspecific with peribronchial ground-glass opacity. Infection can progress rapidly to consolidation and masses, and it can involve both lungs. Because of the angioinvasive nature of the disease, pulmonary necrosis is common. It can appear as a reverse halo at CT and correlates with necrosis found at pathologic analysis. Delays in treatment are associated with a greater mortality rate, and empiric treatment is often necessary before histologic identification and culture. Therefore, knowledge of the risk factors and imaging appearances is necessary for the radiologist to suggest the correct diagnosis.

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