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43

Fungal Diseases

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There are more than 40 species of fungi that affect the lung. Fungi that can readily adapt to the environment of the human lung are highly pathogenic, and the four most pathogenic species are *Histoplasma capsulatum*, *Coccidioides immitis, Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*. Thermal dimorphism is exhibited by all highly pathogenic fungi and by a less common agent, *Sporothrix schenckii*. These fungi change from a mycelial form in nature to a budding, yeastlike structure in infected tissues.

Of the fungal species that infect debilitated patients, five account for most infections: *Aspergillus fumigatus, Candida albicans*, *Pneumocystis carinii*, *Rhizopus arrhizus*, and *Cryptococcus neoformans*. *P. carinii* is discussed in Chapter 45. Rare fungal infections of normal and debilitated hosts and protothecosis are also discussed. *Prototheca* is an achloric genus of alga that is easily mistaken for a fungus because of its morphology and staining characteristics. *Prototheca* organisms are unicellular protophytes, they are to the plant kingdom what protozoans are to the animal kingdom. Protophytes represent the lowest division of the vegetable world and comprise algae, fungi, lichens, and slime molds.

FUNGAL INFECTIONS IN NORMAL AND DEBILITATED HOSTS

Histoplasmosis

H. capsulatum is a soil-inhabiting dimorphic fungus with a worldwide distribution. Most cases are reported from the continental United States, Puerto Rico, and Mexico. It is primarily a rural disease, but exposure to contaminated bird or bat droppings in any setting is a significant risk factor. Mycelia of *H. capsulatum* possess tuberculate chlamydospores. The spores are inhaled and transformed by the heat of the body into yeast forms, presumably by gene stimulation.[1] *H. capsulatum* var *duboisii*, the agent of African histoplasmosis, is considerably larger than *H. capsulatum* and only rarely causes pulmonary infection.

Most persons infected with *Histoplasma* species are asymptomatic. In the healthy host, the severity of clinical disease increases with the size of the infective dose. The major defense against *H. capsulatum* is cell-mediated immunity, and persons with inherited or acquired immune defects suffer more severe disease.

The most prevalent clinical presentation is that of a mild pneumonitis with minimal pulmonary infiltrates, followed by complete healing or formation of a residual fibrocaseous nodule. Chest radiographs obtained during the healing phase usually show one or more oval or irregular, laminated or stippled lesions with various degrees of calcification. Radiographic demonstration of multiple, large calcifications in the lung and hilar lymph nodes is far more common than in tuberculosis.

Patients who develop progressive pulmonary infections can manifest fever, productive or nonproductive cough, dyspnea, weakness, and fatigue. The chest radiograph can demonstrate interstitial, nodular, fluffy, or dense infiltrates. Most of these patients have multilobar disease, but some have lobar infiltrates that mimic lobar bacterial pneumonia. Pulmonary nodules can persist through cycles of increasing and decreasing size. Hilar adenopathy is a common finding.

Rarely, histoplasmosis presents as a pneumonic infiltrate accompanied by striking peripheral eosinophilia reminiscent of the Loeffler syndrome. Patients with old calcified nodules may have a recurrence of the disease. A calcified lymph node can erode into a bronchus and produce a broncholith or cause hemoptysis or recurrent pneumonia. The lungs of patients with residual histoplasmosis contain one or more fibrocaseous granulomas with calcification (Color Fig. 43-1).

In the early stages of infection, macrophages quickly engulf the inhaled spores of *H. capsulatum*, wherein they convert to yeast forms. The lymphocytes of patients with healthy immune systems produce cytokines that activate macrophages and induce formation of granulomas.[2] Microscopic examination reveals fibrocaseous nodules speckled with dystrophic calcification. Yeast cells of

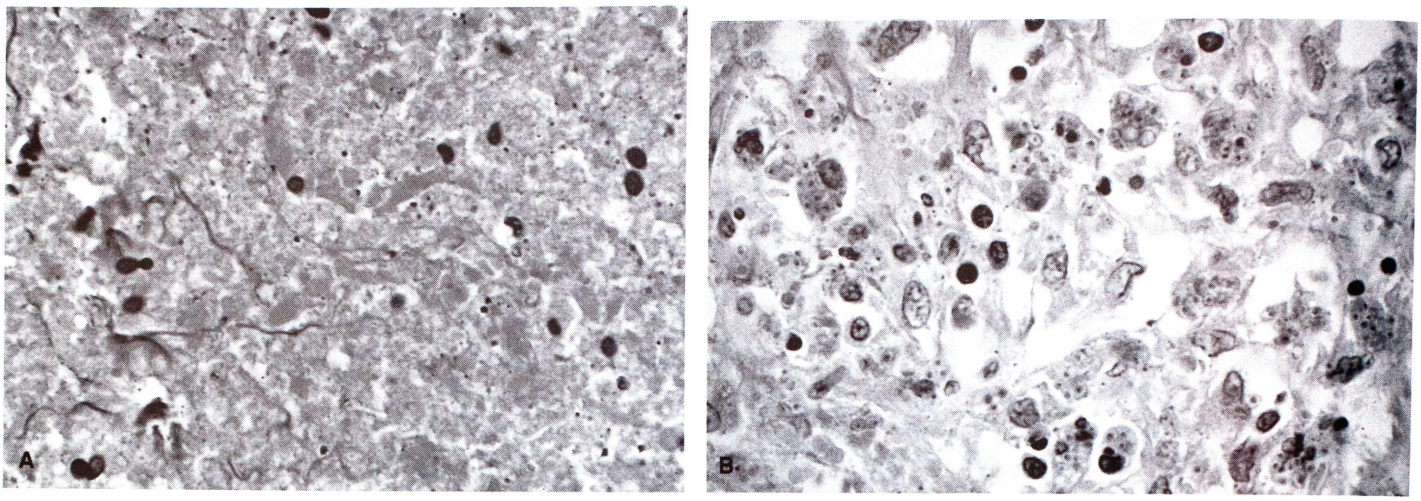

FIGURE 43-1. (**A**) Several yeast cells of *Histoplasma capsulatum* have typical narrow-neck budding and collapsed forms within the center of a necrotic granuloma, as depicted in Color Figure 43-1. (GMS stain; intermediate magnification.) (**B**) Disseminated histoplasmosis in an immunosuppressed patient shows numerous intracytoplasmic *H. capsulatum* organisms. The differential diagnosis includes leishmaniasis, toxoplasmosis, and microsporidiosis. (H & E stain; high magnification; courtesy of P. Angritt, M.D., Washington, DC.)

H. capsulatum may be plentiful or sparse and commonly occur at the soft, necrotic center of the fibrocaseous nodule. The yeast cells are a uniform 2 to 4 μm in diameter and reproduce by narrow-neck budding. Collapsed yeast forms are characteristic, although not pathognomonic (Fig. 43-1*A*).

In infiltrative disease, the organism is demonstrated by hematoxylin and eosin (H & E) stain in macrophages. On H & E stain, *H. capsulatum* has a vacuolated cytoplasm and an eccentric nucleus. (Fig. 43-1*B*). Each organism is surrounded by a clear halo or false capsule, which is a fixation artifact. *H. capsulatum* is demonstrated by Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains and may be acid-fast using Ziehl-Neelsen stain. *H. capsulatum* var *duboisii* yeast cells are 6 to 12 μm in diameter and divide by narrow-neck budding, often producing an hourglass configuration.

The diagnosis of histoplasmosis is best made by culture of the sputum, bronchoalveolar lavage fluid, or tissue. The diagnosis is usually made by serologic testing.[3,4] *Histoplasma* antibodies can be detected in serum and urine; a DNA antigenic probe is available.[5] No treatment is needed for most patients with acute mild pneumonitis, but treatment is recommended for patients with severe, persistent, or progressive disease and for immunosuppressed patients. Amphotericin B remains the drug of choice in all patients, although imidazoles are effective for normal hosts.[6] Surgical intervention is needed for patients who develop mediastinal fibrosis, obstructive lymph nodes, or broncholith-induced bleeding.

Coccidioidomycosis

C. immitis is a dimorphic fungus that occurs endemically in the southwestern United States, where the soil is arid and alkaline and the ambient temperature is usually higher than 26.6°C. This area includes Texas, Arizona, New Mexico, Nevada, California, and Utah. Infection with this organism also occurs in Mexico, Central and South America, Italy, Australia, Romania, and Japan.

There are four clinical manifestations of pulmonary coccidioidomycosis: acute pneumonitis, chronic cavitary disease, pulmonary nodule, and miliary pulmonary disease. Ninety-five to ninety-nine percent of these patients present with acute pneumonia, which is self-limited.[7] Patients with acute infections have pleuritic chest pain, high fever, malaise, dyspnea, and anorexia. A fine, generalized, pink, macular skin rash develops in approximately 50% of patients. Cutaneous hypersensitivity develops in as many as 30% of persons, especially women, and manifests as erythema nodosum or, less commonly, as erythema multiforme with arthralgias or myalgias. Eosinophilia occurs frequently. Chest radiographs usually show segmental pneumonia; hilar adenopathy and pleural effusion are less common. Acute pneumonia can become persistent in patients with underlying disease or immunosuppression and may become life threatening. Rarely, patients with no known immune alterations develop chronic, progressive pneumonia that clinically resembles tuberculosis.

Cavitary disease can occur after an acute primary infection and may persist. The patient may be asymptomatic or have a low-grade fever and hemoptysis. The radiographs typically show thin-walled, 2- to 4-cm cavities. Spontaneous closure is common. Rarely, cavities rupture into the pleural space, producing pneumothorax or empyema.

Some persons develop asymptomatic pulmonary lesions or coccidioidomas, which are solitary, calcific nodules presenting as coin lesions on radiographs. Miliary disease reflects a massive, blood-borne dissemination to all lung fields and usually occurs in immunocompromised patients, such as diabetics, acquired immunodeficiency syndrome (AIDS) patients, and those undergoing immunosuppressive therapy. *C. immitis* infection less commonly presents as a fungus ball mimicking an aspergilloma.

The host defense against *C. immitis* is delayed-type immunity, similar to that against *Histoplasma* species; therefore, the histologic changes seen in the normal host are also similar. Granulomas initially have central suppuration with caseating necrosis (Color Fig. 43-2). Late lesions become fibrocaseous. Fungi are found in necrotic areas (Figs. 43-2 and 43-3), and spherules containing endospores are pathognomonic. Spherules are 20 to 80 μm in diameter and contain 1- to 5-μm endospores (Color Fig. 43-3). Ruptured spherules release endospores that lie free in the tissue and are differentiated from *H. capsulatum* by their lack of

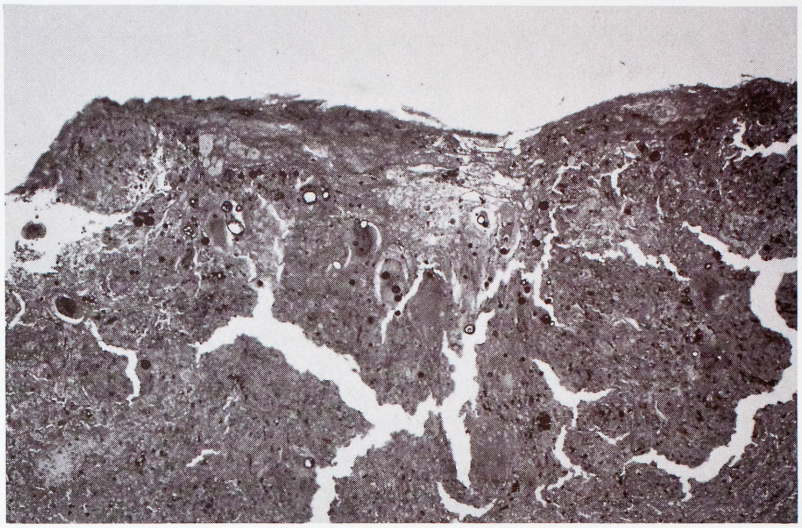

FIGURE 43-2. A microscopic view of a fibrocaseous nodule of coccidioidomycosis shows numerous fungal organisms of various sizes. (GMS stain; low magnification; courtesy of P. Angritt, M.D., Washington, DC.)

budding and great variation in size. Septate hyphae, 3 to 5 μm wide, frequently occur in pulmonary cavities.

The diagnosis can occasionally be made by identifying spherules in sputum, but it is usually established serologically, with complement fixation and precipitation tests.[8–11] No treatment is needed for most patients with acute pulmonary coccidioidomycosis, but amphotericin B is the drug of choice for chronic or cavitary disease. Imidazoles are reasonable alternatives for life-threatening illness.[12]

Blastomycosis

B. dermatitidis is a soil-inhabiting, dimorphic fungus that is remarkably difficult to isolate. It is a cause of disease in persons living in or visiting the central and southeastern United States; infection also occurs in Canada, Mexico, the Middle East, Africa, and India.[13]

Pulmonary blastomycosis has several clinical presentations. Most often it presents as an abrupt illness with productive cough, headache, chest pain, weight loss, fever, abdominal pain, night sweats, chills, and anorexia. Some patients present primarily with pleuritic chest pain. Chest radiographs reveal lobar consolidation, multilobar infiltrates, perihilar infiltrates, multiple nodules, or miliary infiltrates. The upper lobes are most frequently involved. The process may resolve spontaneously, persist, or progress to a chronic lesion with fibrosis and cavitation.

In the normal host, the lung lesions of blastomycosis are suppurative granulomas (Fig. 43-4). Macrophages have a limited ability to ingest and kill *B. dermatitidis*, and the persistence of the yeast cell antigens leads to continued recruitment of neutrophils.[14] In tissue, *B. dermatitidis* is a round, 5- to 15-μm yeast cell that divides by broad-based budding (Fig. 43-5). It has a thick, double-contoured cell wall and multiple nuclei. The organisms are slightly mucicarmine positive. There is a small strain of *B. dermatitidis*, similar in size to *H. capsulatum*, and there is a form as large as 30 μm in diameter, but they are rare.

The diagnosis is established by culture or by examination of biopsy material. Most current serologic tests have many false nega-

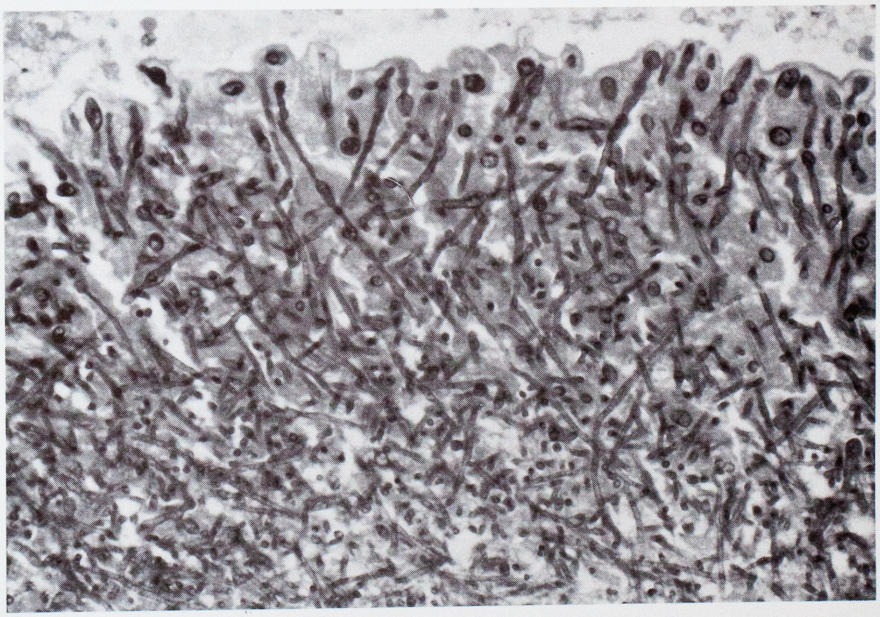

FIGURE 43-3. *Coccidioides immitis* septate hyphae are 3 to 4 μm wide with frequent swellings. (GMS stain; intermediate magnification.)

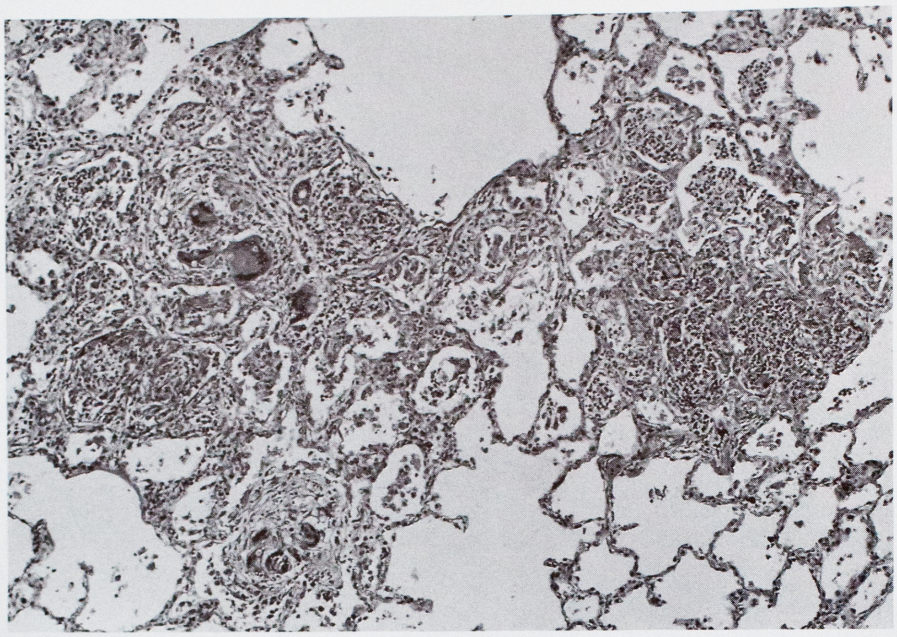

FIGURE 43-4. A pyogranulomatous lesion is seen in the lung of a patient with blastomycosis. (H & E stain; low magnification.)

tives and are not very useful, but more specific tests are being developed.[15] Imidazoles are useful for treating mild disease; Amphoteracin B is best for treating severe disease.

Paracoccidioidomycosis

P. brasiliensis is a dimorphic fungus that produces a primary pulmonary infection.[16] The initial lesion is frequently inapparent, but it can evolve into a chronic granulomatous disease of the buccal and nasal mucosa with extension to the skin and, less often, to the gastrointestinal tract. Lymph node and spleen involvement are common, but dissemination to multiple organs is rare. Paracoccidioidomycosis occurs in South and Central America; most patients are men with occupational exposures to soil.

P. brasiliensis infection is usually asymptomatic or manifests as a mild, productive cough. Persons migrating to endemic areas develop minor lung changes and skin test reactivity. Chest radiographs commonly show mild, bilateral, patchy or circumscribed infiltrates in the perihilar regions. Cavitary lesions occur in about one third of patients. Acute, progressive disease is uncommon, except in immunocompromised persons, in whom rapid consolidation occurs and the course is fulminant and fatal.

At necropsy, the lungs of patients with chronic, progressive pulmonary disease have a cobblestone appearance. The cut surface usually shows miliary granulomas and peripheral fibrosis. At a later stage in the disease, linear fibrosis radiates from the hilum, and there are associated emphysematous changes. Cavitary lesions develop in some patients.

In benign primary pulmonary paracoccidioidomycosis, there is an initial alveolitis with macrophages, giant cells, and an influx of numerous neutrophils. Granuloma formation occurs later; the center of the granuloma is initially suppurative (Fig. 43-6), later caseous, and finally fibrocaseous. Unlike the fibrocaseous granulomas of *Histoplasma* species, those of *P. brasiliensis* are not cal-

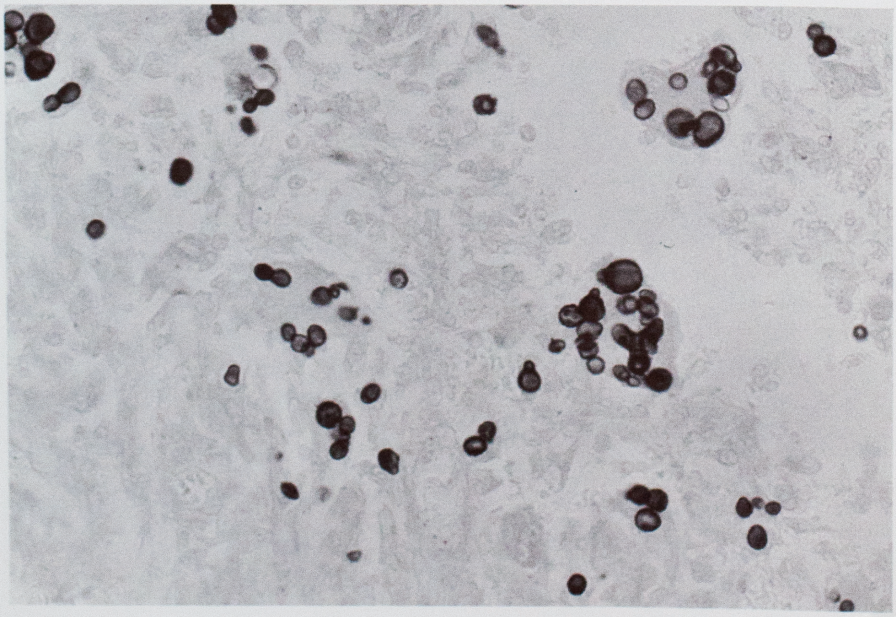

FIGURE 43-5. *Blastomyces dermatitidis* yeast cells in the lung demonstrate broad-based budding and great variation in size. (GMS stain; intermediate magnification.)

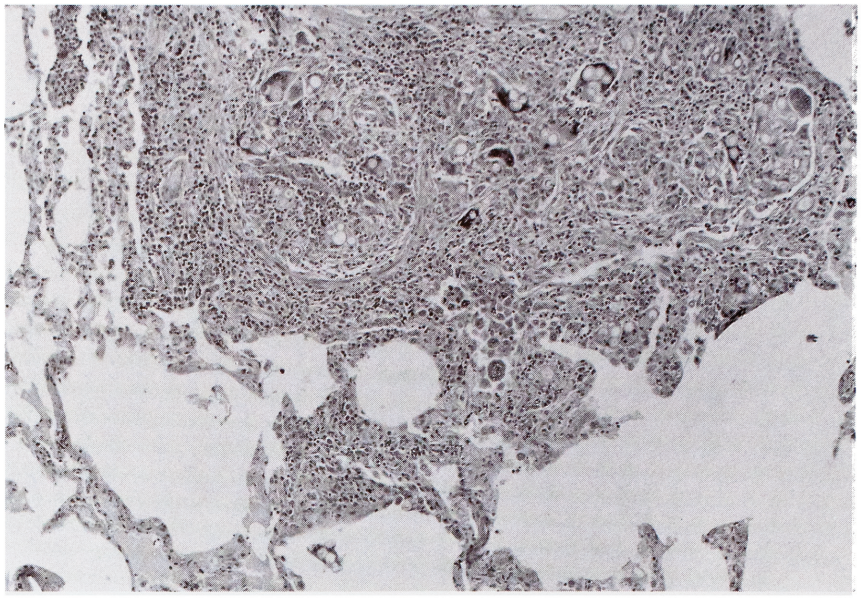

FIGURE 43-6. Pyogranulomatous lesion in the lung of a patient with paracoccidioidomycosis (*i.e.*, South American blastomycosis). (H & E stain; low magnification.)

cified. In active granulomas, yeast cells are found within the giant cells and macrophages. In older granulomas, the yeast cells are found most often at the interface between the necrosis and the epithelioid cells. The yeast cells vary considerably in size (*e.g.*, 5–30 μm) and shape, and they usually have thin walls with no internal structure. Larger yeast cells may have thicker walls. Demonstration of the typical multiple-budding yeast cells is necessary for a tissue diagnosis (Fig. 43-7). Ketoconazole is the treatment of choice.

Sporotrichosis

S. schenckii is a dimorphic fungus that occurs worldwide. It usually presents as an ulcerated lesion of the hand. In the United States, most infections occur in the Midwest river valley area and in Oklahoma, but the organism is also common in Mexico and Central America. All age groups may be affected, but the infection occurs most commonly in adults. Patients may develop pulmonary sporotrichosis directly or by hematogenous spread from the skin lesion.[17] Many patients with pulmonary sporotrichosis are alcoholics, suggesting bronchial aspiration as the source of lung infection. Disseminated infections are rare, but bone involvement is well recognized. Rarely, sporotrichosis may present as a fungus ball mimicking an aspergilloma. A related fungus, *Sporothrix cyanescens*, rarely causes pulmonary disease.[18]

Patients with pulmonary sporotrichosis usually have a productive cough, malaise, weight loss, and low-grade fever; hemoptysis is rare. Chest radiographs are nonspecific but often reveal hilar adenopathy and cavitation. Pleural involvement is rare.[19] The lungs show large, apical granulomas bilaterally, some of which may cavitate.[20] Microscopically, the granulomas often have central suppuration or caseation (Fig. 43-8), but it can be nonnecrotizing. Fibrocaseous granulomas rarely occur, but unlike those of *Histoplasma* species, they lack calcification.

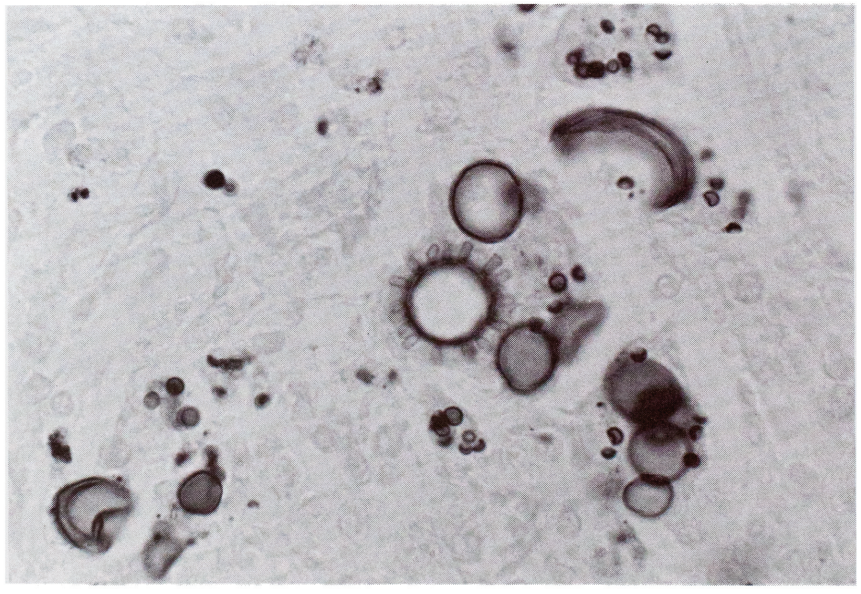

FIGURE 43-7. *Paracoccidioides brasiliensis* yeast cells demonstrate marked pleomorphism, great variation in size, and multiple peripheral budding. Notice the characteristic spoke-wheel sporulation. (GMS stain; intermediate magnification.)

FIGURE 43-8. Necrotizing granulomatous inflammation in the lung of patient with sporotrichosis. (H & E stain; low magnification.)

S. schenckii presents as spherical, oval, or elongated yeast cells. Round or oval cells are approximately 3 to 6 μm in diameter (Fig. 43-9). Elongated forms can measure 3 μm wide by 10μm long. Budding is irregular, but narrow-neck, budding is most common. The asteroid body (Color Fig. 43-4) is a frequent finding in cases of sporotrichosis from South Africa and Japan, but it is uncommon in cases from the Western Hemisphere. Although not pathognomonic, it provides presumptive evidence of the disease.

The diagnosis of pulmonary sporotrichosis depends on isolation of the fungus from sputum, bronchial washings, or lung tissue or on demonstration of the characteristic yeast cells.[21] Serologic antibody tests (*e.g.*, slide latex agglutination test) can confirm the diagnosis and determine the effectiveness of therapy.[22]

COMMON FUNGAL INFECTIONS OF DEBILITATED HOSTS

Several diseases are caused by fungi that are normal inhabitants of the environment. They produce disease in immunocompromised hosts with uncontrolled diabetes mellitus, burns, human immunodeficiency virus infection, cancer, organ transplants, babies with low birth weights, malnutrition, and therapeutic interventions, such as antibiotic therapy, steroids, and hyperalimentation.

Aspergillosis

There are almost 900 species belonging to the genus *Aspergillus*, but only about 10 species are implicated in human infections: *A.*

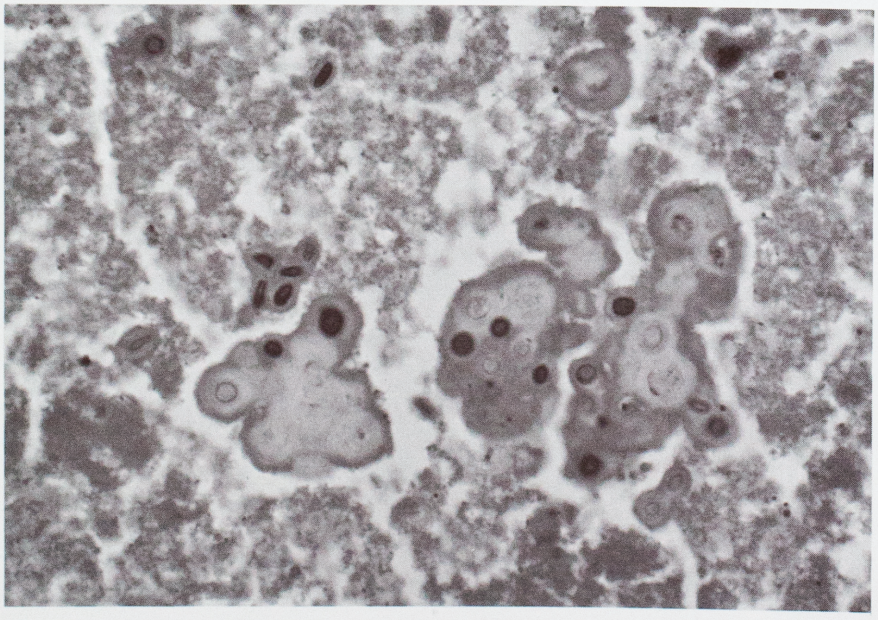

FIGURE 43-9. Yeast cells of *Sporothrix schenckii* are found in a necrotizing area of lung. Notice the surrounding smooth matrix and elongated forms. (GMS stain; intermediate magnification.)

fumigatus, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus niveus*, *Aspergillus nidulans*, *Aspergillus ochraceus*, *Aspergillus deflectus*, *Aspergillus restrictus*, and *Aspergillus clavatus*. *A. fumigatus* is the most frequent cause of allergic and invasive aspergillosis. *A. flavus* is probably the most common cause of disseminated disease. Three separate presentations of pulmonary aspergillosis are known: allergic bronchopulmonary aspergillosis, aspergilloma, and invasive aspergillosis. Allergic bronchopulmonary aspergillosis is a reaction to the conidia or spores of *Aspergillus* organisms. It can manifest as an allergic asthmalike reaction or as extrinsic allergic alveolitis. Conidia are asexually produced reproductive spores that typically do not germinate. Allergic bronchopulmonary aspergillosis is one of the more common causes of pulmonary eosinophilia.

An aspergilloma or fungus ball results from the colonization of preformed cavities produced by other diseases or from chronic allergic bronchopulmonary aspergillosis. The characteristic clinical feature is recurrent, mild to severe hemoptysis. Classically, the chest radiographs reveal a uniform, round to oval opacity with a radiolucent crescent (*i.e.*, Monod sign). Invasive aspergillosis is rare. It can arise *de novo* or from progression of an aspergilloma or allergic aspergillosis. Invasive aspergillosis presents clinically as a rapidly advancing necrotizing pneumonia, frequently with a pleuritic friction rub.

The pathologic changes of allergic bronchopulmonary aspergillosis are those of bronchiectasis, segmental collapse, and fibrosis. Hyphae can be found in mucus plugs with abundant inflammation of the bronchi. In an aspergilloma, the fungus grows in a multilayered fashion within a cavity as one or more brown balls composed of tangled masses of mycelia. Old cavities show liquefied dead hyphal elements, giant cells, and abundant oxalate crystals. The characteristic pattern of invasive aspergillosis consists of numerous hyphae radiating from a central focus with extensive necrosis of the surrounding lung parenchyma.[23] The hyphae have a marked tendency to invade blood vessels and cause thrombosis, producing an acute, necrotizing, pyogenic pneumonia (Fig. 43-10).

The hyphae of *Aspergillus* organisms are 2 to 5 μm in diameter and septate, and they typically demonstrate dichotomous branching arising regularly at a 45° angle (Color Fig. 43-5; Fig. 43-11). The hyphae usually stain well with hematoxylin and eosin, and vacuoles are frequently observed. Conidial heads forming at the end of conidiophores (Color Fig. 43-6) occasionally occur in pulmonary lesions, and the species of *Aspergillus* can frequently be determined by the morphologic features of the conidial heads.

Systemic antifungal agents are of no benefit in allergic aspergillosis, and patients are best treated with glucocorticoids and bronchodilators. Aspergillomas may produce a fatal exsanguinating hemorrhage, and aggressive surgical resection is recommended.[24] Invasive aspergillosis is often rapidly fatal, but early diagnosis and treatment with combinations of amphotericin B, 5-fluorocytosine, and rifampin can be effective.

Candidiasis

Candida species are common inhabitants of mucocutaneous tissues but can overgrow and invade when host defenses are depressed. *Candida* species are found worldwide, but the most virulent species are *C. albicans* and *Candida tropicalis*. The host defense against *Candida* organisms depends largely on neutrophils, and children with chronic granulomatous disease are particularly prone to this infection.

The gross changes of pulmonary candidiasis vary, and the lungs may have patchy or diffuse areas of consolidation, most frequently in the lower lobes (see Chap. 45; see Figs. 45-14 and 45-15). Round, well-circumscribed, yellow-gray, miliary nodules with peripheral hemorrhagic rims are seen in patients with hematogenous dissemination.[25] Children with embolic pulmonary candidiasis exhibit foci of infarction that infrequently cavitate.

Microabscesses are identified with yeast cells, pseudohyphae, and hyphae among neutrophils. In specimens from granulocytopenic patients, coagulative necrosis and hemorrhage are observed. Chronic, indolent infections and those treated with antifungal therapy may become granulomatous. The yeast cells are round or

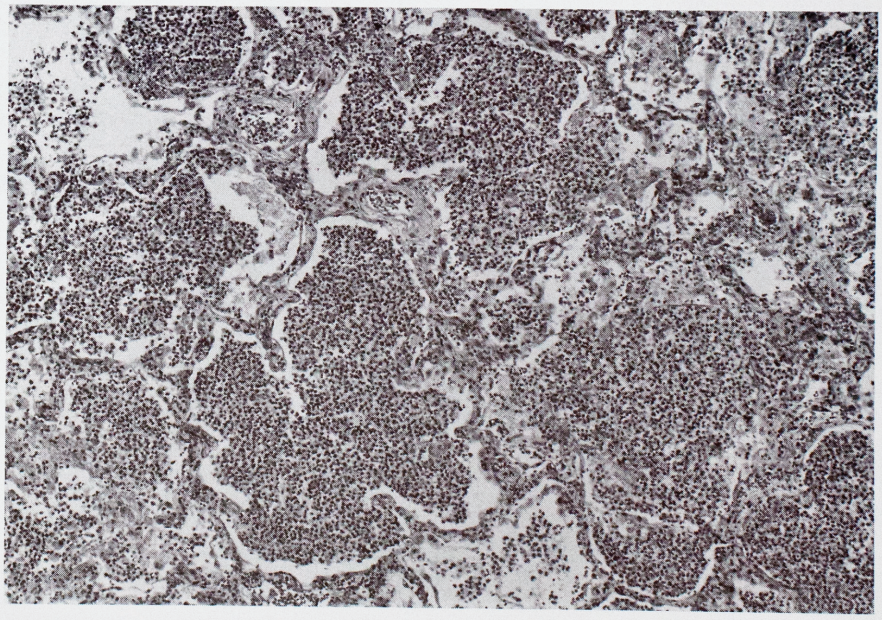

FIGURE 43-10. The necrotizing bronchopneumonia is caused by *Aspergillus* organisms. (H & E stain; intermediate magnification.)

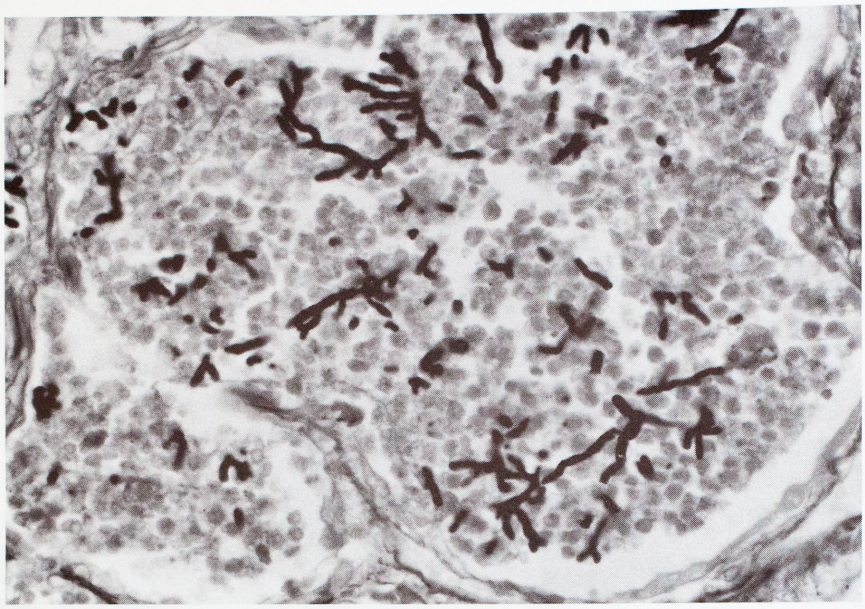

FIGURE 43-11. Numerous hyphae of *Aspergillus* organisms are seen in the alveolar exudate. The prominent dichotomous branching is characteristic of *Aspergillus* infection. (GMS stain; low magnification.)

oval, are 3 to 4 μm in diameter, and contain one or more vacuoles. They are usually in various stages of budding, and the formation of germ tubes is common. The pseudohyphae or hyphae are 3 to 5 μm wide and demonstrate irregular branching. *Candida* organisms stain well with hematoxylin and eosin, Brown-Hopps tissue Gram stain, GMS, Gridley, and PAS. Species identification cannot be made in hematoxylin and eosin–stained sections, but immunohistochemistry with monoclonal antibodies helps speciation.

Pneumocystis carinii *Pneumonia*

P. carinii pneumonia is discussed in Chapter 45, which deals with the pulmonary disorders associated with AIDS.

Zygomycosis

Zygomycosis and mucormycosis are clinical terms for infection caused by fungi of the order Mucorales. The most common agent of human zygomycosis is *R. arrhizus*.[26] The Mucoraceae are ubiquitous and are known as bread molds, because they live on decaying breads and fruits. Lung disease is acquired by inhalation, aspiration, or hematogenous spread. *Absidia corymbifera* is the second most common cause of pulmonary zygomycosis. Zygomycetes genera infrequently implicated in pulmonary disease include *Mucor*, *Conidiobolus*, *Rhizomucor*, *Cunninghamella*, *Mortierella*, *Apophysomyces*, and *Saksenaea*.

Characteristically, the lungs in a patient with zygomycosis have patchy or solid zones of consolidation with areas of infarction that sometimes cavitate. The Mucoraceae invade blood vessels, producing thrombosis surrounded by infarction necrosis (Color Fig. 43-7). The fungi have randomly branched, 10- to 15-μm-wide hyphae that are rarely septate and stain well with hematoxylin and eosin, PAS, and GMS stains.

Cryptococcosis

C. neoformans is a ubiquitous, soil-inhabiting fungus that is most plentiful in areas where birds, especially pigeons, are abundant. The mode of entry is thought to be the respiratory tract. *Cryptococcus* organisms produce severe disease in persons with defective delayed immune mechanisms, but even healthy people acquire the disease after large numbers of organisms are inhaled. Two other species of *Cryptococcus*, *Cryptococcus albidus* and *Cryptococcus laurentii*, infrequently cause human disease.

Pulmonary cryptococcosis is far more common than cryptococcal meningoencephalitis but is diagnosed less often because it is usually transient and produces few or no symptoms.[27,28] Chest radiographs usually show lower lobe involvement, especially on the right side. Some patients with fulminant disease develop the adult respiratory distress syndrome.

The lungs of patients with asymptomatic or mildly symptomatic, self-limited pulmonary cryptococcosis have one or more round, noncalcified, fibrocaseous nodules, which are usually subpleural. The lungs of patients with progressive pulmonary cryptococcosis can have a variety of pathologic changes, including single or multiple nonfibrous nodules, segmental or lobular consolidation, and less commonly, hilar adenopathy. The upper lobes usually are more extensively involved in patients with progressive disease. Diffuse interstitial, peribronchial, or miliary changes, imparting a slick, glistening, and slimy consistency to the lungs are seen in profoundly immunodeficient patients. The host reaction to *C. neoformans* varies with the degree of cell-mediated immunodeficiency. The cryptococcal lesions range from anergy with no reaction to abscess formation and fibrocaseous granulomas. In the lungs of patients with self-limited pulmonary cryptococcosis, the initial lesion is a focal suppurative reaction that resolves or progresses to a fibrocaseous granuloma. The yeast cells in granulomatous lesions occur predominantly within giant cells and macrophages. Yeast cells often have a prominent mucinous capsule that stains bright red with the Mayer mucicarmine stain (Color Fig. 43-8) and bright green with Movat stain.

RARE FUNGAL INFECTIONS OF NORMAL HOSTS

Adiaspiromycosis

Chrysosporium parvum and *C. parvum* var *crescens*, formerly *Emmonsia crescens*, cause adiaspiromycosis if large numbers of conidia are inhaled.[29,30] They do not multiply or disseminate in human tissue,

but they induce a granulomatous reaction. Histologically, adiaspores (*i.e.*, adiaconidia) as large as 600 μm in diameter are centered in noncaseating or suppurative granulomas (Color Fig. 43-9). The adiaspores have thick (*i.e.*, 20–70 μm), multilayered walls and stain well with hematoxylin and eosin. The diagnosis is established histologically; cultures, skin testing, and diagnosis using bronchoalveolar lavage are not recommended.

Rhinosporidiosis and Beauveria bassiana *Infection*

Rhinosporidium seeberi, the causative organism of rhinosporidiosis, elicits a chronic hyperplastic inflammatory response of the skin, nose, nasal passages, and rarely, the bronchi; the disease is more common in younger persons.[31,32] Mature spherules are large, measuring up to 350 μm in diameter, and contain endospores that are 2 to 10 μm in diameter. Trophocytes are smaller (10–125 μm) and do not contain endospores.

Beauveria bassiana, a cause of pulmonary mycosis in tortoises and alligators, rarely produces cavitary lung lesions in humans.[33,34] Culture is necessary to confirm the diagnosis.

RARE FUNGAL INFECTIONS OF DEBILITATED HOSTS

Pseudoallescheria boydii *Infection*

Pseudoallescheria boydii, the major cause of mycetoma in the United States, can cause three kinds of lung lesions: abscesses, cavitary lesions, or fungus balls. *P. boydii* is an increasingly important cause of pulmonary infection in the immunocompromised patient, and the lung lesion usually is a fungus ball (*i.e.*, pseudoallescherioma) consisting of matted collections of fungal hyphae. The hyphae are septate, 2 to 5 μm wide, and similar to those of *Aspergillus* organisms. Fungal invasion and thrombosis of blood vessels produces nodular infarctions that become the fungus ball.[35] Species of *Acremonium*, another fungus isolated in patients with mycetoma, can also produce invasive pulmonary disease in immunocompromised hosts.[36]

Blastoschizomyces capitatus *Infection*

Blastoschizomyces capitatus, formerly *Trichosporon capitatum*, is a rare cause of invasive fungal disease in immunocompromised hosts. Pulmonary infiltrates can progress to mycetomalike cavitations.[37]

Phaeohyphomycosis

Pulmonary phaeohyphomycosis can occur in immunocompromised hosts. Systemic phaeohyphomycosis usually begins with a pulmonary lesion and typically disseminates to the brain. *Xylohypha bantiana*, a dematiaceous fungus that is primarily neurotropic and also infects skin and subcutaneous tissues is the most commonly encountered agent of pulmonary phaeohyphomycosis.[38] *Alternaria* (Color Fig. 43-10) and *Curvularia* species have also been implicated as causes of invasive pulmonary phaeohyphomycosis. Patients have granulomatous lung nodules containing dark hyphal fragments.

Penicillium *Infection*

Penicillium species are ubiquitous, blue-green molds that are common, incidental commensals of sputum and bronchial secretions of healthy hosts. *P. marneffei* is the only known species to cause disease in humans, primarily external otitis, but it may also cause an allergic bronchopulmonary disease.[39] Invasive pulmonary disease can occur in immunosuppressed patients.[40] Histologic examinations of rare cases show vascular invasion, thrombosis, and infarction, producing pulmonary cavities with fungus balls. *P. marneffei* in tissue sections usually appears as a spherical, oval, or elongated yeast cell as long as 20 μm and containing a transverse septum.

Malassezia furfur *Infection*

Malassezia furfur, the agent of pityriasis versicolor, has produced systemic infections in patients receiving intravenous lipid therapy.[41] Neonates with cardiovascular disease and adults with immunosuppression or intestinal disease are especially susceptible.[42] Pulmonary infiltrates are identified on chest radiographs, and biopsies show congestion, marked acute and chronic inflammation, vasculitis, numerous yeast cells, and rare hyphae (Fig. 43-12). The yeast cells are thin walled and 2 to 5 μm in diameter; the hyphae are short and 2 to 4 μm wide, and they form chains.

Trichosporon beigelii *Infection*

Trichosporon beigelii, the agent of white piedra, can cause pulmonary infection in immunocompromised patients.[43] Neutropenia and malignancy are significant risk factors.[44–46] Biopsy shows mycotic thromboembolic vasculitis with budding yeast cells, hyphae, and arthroconidia. Hyphae are thick walled and closely septate. The septate hyphae fragment into oval or rectangular arthroconidia that are approximately 2 to 4 μm × 3 to 9 μm.

Torulopsis glabrata *Infection*

Torulopsis glabrata, a common yeast of skin, can produce opportunistic pulmonary infections.[47] The host response varies from marked suppuration to virtually no reaction. *T. glabrata* may be centered among neutrophils or occur intracellularly within macrophages. The yeast cells can be difficult to differentiate from *Histoplasma capsulatum*, but *T. glabrata* yeast cells are slightly larger (*i.e.*, 2–5 μm), are more pleomorphic, and have a broader bud attachment.

Saccharomyces cerevisiae *and Other Infections*

Saccharomyces cerevisiae, the beer yeast, and *Fusarium* spp., *Rhodotorula rubra, Kluyveromyces fragilis, Scopulariopsis brevicaulis, Geotrichum candidum*, and *Schizophyllum commune* are ubiquitous fungi that often contaminate skin, urine, and feces and infrequently produce opportunistic pulmonary infections.[48–55] These infections can be fatal.

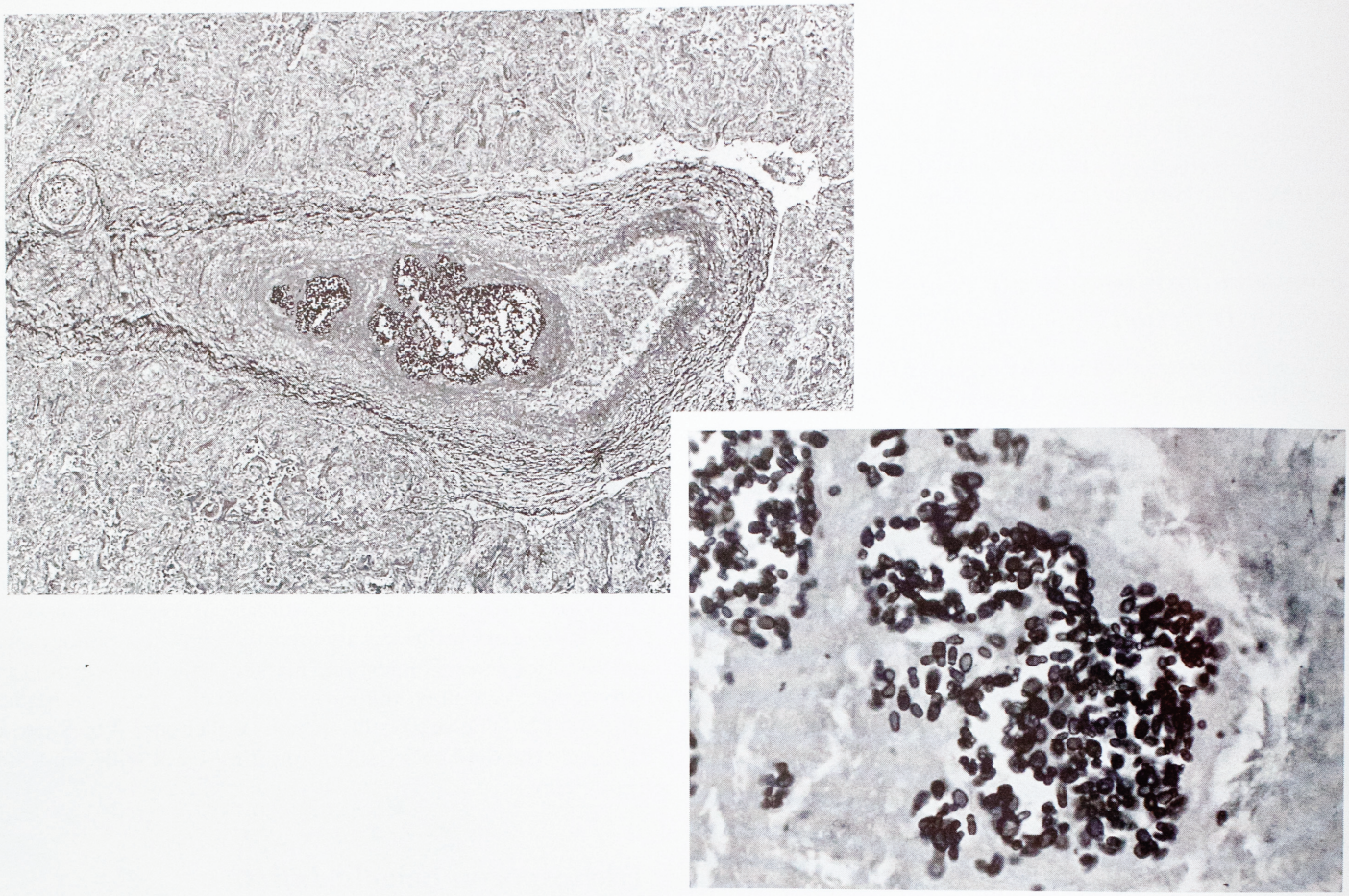

FIGURE 43-12. Vascular invasion in the lung of a patient with *Malassezia furfur* shows colonies of yeast cells within a blood vessel. (GMS stain; low magnification.) Yeast cells in greater detail (*inset*). (GMS stain; intermediate magnification.)

PROTOTHECOSIS

Prototheca species are achloric algae that cause protothecosis, and *Prototheca wickerhamii* accounts for most infections in humans. It is an uncommon disease that frequently involves the olecranon bursa, causing a necrotizing chronic inflammation. In immunocompromised hosts, it rarely causes systemic infections.[56] In tissue sections, *P. wickerhamii* are round to oval, 3- to 15-μm-diameter cells that have thick walls and stain intensely with GMS, PAS, and Gridley stains. They divide by internal sporulation, producing characteristic morular configurations.

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