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Pulmonary Pathology in Acquired Immunodeficiency Syndrome

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The acquired immunodeficiency syndrome (AIDS) represents a constellation of clinicopathologic manifestations resulting primarily from infection by the human immunodeficiency virus (HIV). HIV infection produces an unrelenting, progressive impairment of cell-mediated immunity that makes patients susceptible to a variety of opportunistic infections and prone to developing malignant tumors. The current definition of AIDS includes adolescents and adults who are seropositive for HIV and have fewer than 200 $\times 10^6$ CD4 T lymphocytes (*i.e.*, helper cells) per liter of peripheral blood and patients with tuberculosis, recurrent pneumonia, or invasive cervical cancer.[1]

At the beginning of the AIDS epidemic, it became clear that the lung was a major target of the disease and that pulmonary processes were the cause of death of most of these patients. Almost 80% of children with HIV infection develop pulmonary problems, and if left untreated, 70% would die within 2 years of diagnosis.[2]

Recognition of the pathologic manifestations of AIDS, particularly in the lung, has become a significant component of the pathologist's practice, especially in the large metropolitan areas of the United States, where most of these patients are concentrated. Most of the infections were covered in previous chapters (see Chaps. 38 through 44); in this chapter we focus on the peculiar behavior and characteristics of these infections in the AIDS population.

PATHOGENESIS OF THE ACQUIRED IMMUNODEFICIENCY SYNDROME

The molecular biology of HIV type 1 infection was the subject of a review by Greene.[3] It is an RNA virus belonging to the Lentivirinae subfamily of retroviruses, known for their propensity to produce protracted indolent infections. The HIV-1 genome is complex and contains at least nine genes. The three major genes are *gag, pol*, and *env*. The *gag* gene encodes core-group–specific antigens, *env* the surface envelope proteins, and *pol* the polymerase of the enzyme reverse transcriptase. Reverse transcriptase can transcribe a single strand of RNA into many copies of double-stranded DNA for incorporation into the genetic material of the host. Other genes include the *vif* gene, which is an infectivity factor, the *rev* gene that acts as a regulation switch for viral growth, the regulatory *tat* gene that enhances viral protein production, and the regulatory *ref* gene that inhibits viral protein production.

Ultrastructurally, the virus is an icosahedral structure containing 72 spikes formed by the two major envelope proteins gp 40 and gp120. The core contains four nucleocapsid proteins, p24, p17, p9, and p7. CD4 T-lymphocytes and monocytes are the main targets of the virus. Binding of gp120 to CD4 lymphocytes results in fusion of the viral envelope and cell membrane. The viral contents are then emptied into the host cell cytoplasm, where the virus may replicate or remain latent. One of 100 CD4 T-cells

contain DNA indicating latency; approximately 1 of 1000 express RNA indicating active replication.

The cytopathic effects of HIV-1 on CD4 lymphocytes are not clear, but fusion of cells with the formation of multinucleated giant cells appears to be one mechanism. An infected CD4 lymphocyte has gp120 and gp40 on its surface, allowing it to bind with other CD4 lymphocytes and form a syncytium of cells that eventually die. The process whereby a singly infected cell may bring about the death of many normal cells is believed to be a significant factor associated with cell destruction and profound immunodeficiency. HIV cofactors may also be important. *Mycoplasma fermentans, incognitus* strain, profoundly enhances the cytocidal effects of HIV-1 infection on human T lymphocytes *in vitro* (Fig. 45-1).[4]

HIV is transmitted primarily by sexual contact, exposure to blood or blood products, by the sharing of contaminated needles among intravenous drug users, factor concentrates in hemophiliacs, organ transplants, transplacentally from mother to child, and rarely in health care workers by accidental needle sticks and breaks in the skin.

FUNGAL, PROTOZOAL, AND HELMINTHIC INFECTIONS

Pneumocystis carinii *Pneumonia*

One cause of pulmonary infection is *Pneumocystis carinii*. There has been debate about whether the organism represents a protozoan or a fungus, but evidence gathered by using RNA probes and Southern blot analysis indicates that *P. carinii* is probably a fungus with a unique unicellular mycelial phase.[5]

Infection produced by *P. carinii* occurs almost exclusively in immunocompromised hosts and invariably produces pneumonia. In 1952, Vanek and Jirovec identified *P. carinii* as the causative agent of outbreaks of pneumonia in malnourished infants and children in European orphanages after World War II.[6] Since then, *P. carinii* has become a well-recognized pathogen in patients immunocompromised by malignancies, prolonged corticosteroid therapy, or organ transplantation.

With the advent of the AIDS epidemic, the incidence of *P. carinii* pneumonia (PCP) has risen dramatically in developed countries. PCP represents the most common manifestation of HIV infection in approximately 60% to 85% of these patients and is often the initial presentation of the disease. It is the main cause of death of about one third of the patients, and the risk of developing PCP in adults with HIV infection rises markedly as the CD4 count falls below 200×10^6/L.[7,8]

Children with PCP have a much poorer prognosis than adults, and the initial infection is often fatal, although their CD4 counts may be higher. PCP is relatively rare in Africa and has not been reported as a cause of pneumonia in Uganda, a country with the highest number of AIDS cases in the world.[9] The reason for this surprising statistic is that *P. carinii* is probably not a part of the environmental flora indigenous to that area. Most patients with PCP present with fever, cough, and shortness of breath. Chest radiographs may be normal; show relatively mild infection with purely interstitial, reticular, or reticulonodular infiltrates throughout both lungs; or also have one or more patchy areas of alveolar consolidation.[10] Extensive, confluent areas of alveolar disease are associated with acute respiratory insufficiency, which is frequently fatal (Fig. 45-2). The duration of symptoms in patients with PCP and HIV infection is longer than in non-AIDS patients, and the clinical manifestations are somewhat different in the two groups.[11]

In lung biopsies, the earliest manifestation is associated with empty alveoli, and with minimal amounts of fibrinous debris but with special stains, individual cysts and trophozoites are seen adhering to the alveolar lining cells (*i.e.*, septal attachment).[10] As the infection progresses, masses of exudative material begin to accumulate within alveoli, eventually resulting in their filling and consolidation. The intraalveolar exudates are lightly eosinophilic and have a characteristic foamy or honeycomb appearance (Fig. 45-3).

The diagnosis is usually established by the demonstration of the organism's cyst, mainly by Grocott's modification of the Gomori methenamine silver stain (GMS). The cysts appear as round or crescent-shaped structures that are 5 to 7 mm in diameter, only slightly smaller than erythrocytes (Fig. 45-4). Darkly staining structures referred to as extracapsular dots are sometimes seen as pairs in the center of the cysts, depending on the cystic orientation.

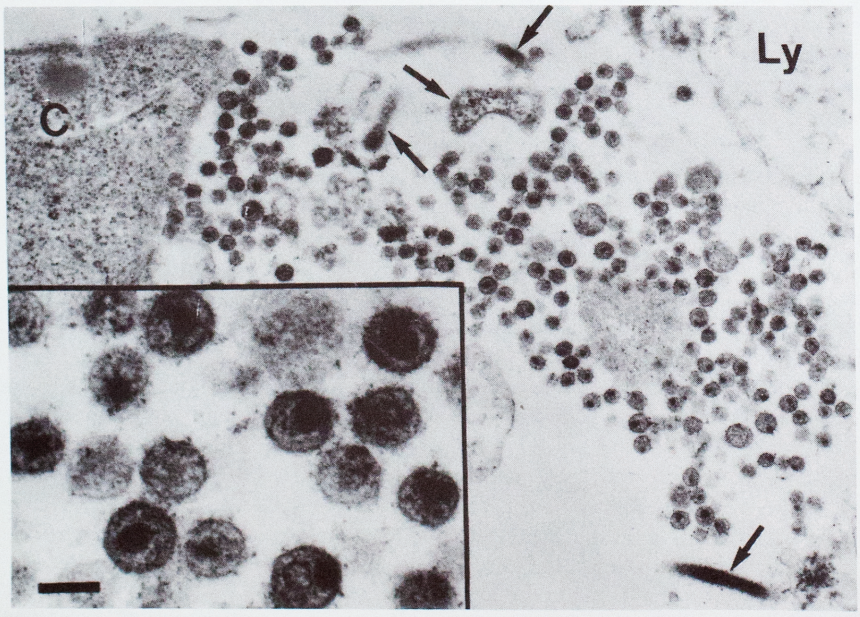

FIGURE 45-1. In an electron micrograph of a cell culture coinfected with human immunodeficiency virus (HIV) and *Mycoplasma fermentens, incognitus* strain, the electron-dense, elongated forms of the *Mycoplasma* organisms are visible (*arrows*). The HIV particles have well-defined cores (*inset*; scale is equal to 100 nm). (C, viable cell; Ly, cell lysed by the effects of the virus; courtesy of S-C Lo, M.D., Washington, DC.)

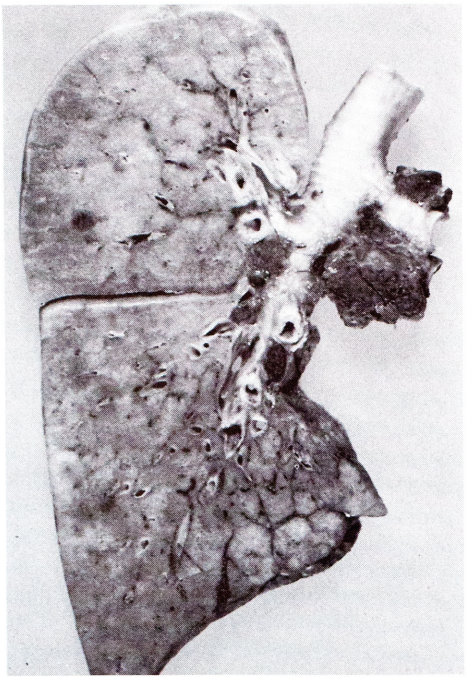

FIGURE 45-2. The characteristic gross appearance of *Pneumocystis carinii* pneumonia in a man with acquired immunodeficiency syndrome includes massive consolidation of the right lung by a pale, firm infiltrate. Enlarged anthracotic hilar lymph nodes are apparent. (From Saldana MJ, Mones JM, Martinez GR. The pathology of treated pneumocystis carinii pneumonia. Semin Diagn Pathol 1989;6:300.)

A focal, dark thickening of the capsule has been interpreted as the "exit door" for the intracystic bodies or sporozoites.[12]

Ultrastructurally, the foamy exudates of PCP consist of large numbers of trophozoites with their microtubular extensions, characteristic cysts, fibrin, and cellular debris.[12] Trophozoites stain well with Romanovsky-type stains such as Giemsa, Wright-Giemsa, and Diff-Quick; the cytoplasm appears blue, the nucleus appears red and is surrounded by a pale halo. Cysts and trophozoites can be seen in the same preparation with AFIP light silver or hematoxylin and eosin stain and Shiota combined GMS and Giemsa method.[13]

Immunoperoxidase stains for both cysts and trophozoites, including their microtubular extensions, are available.[14] Viable and nonviable organisms distorted by therapy react with the antibody and significantly improve the diagnostic yield. The stains are particularly useful for scant cytologic specimens with few organisms and for sputum samples contaminated with *Candida albicans*, which can resemble *P. carinii*.

In patients presenting with massive PCP and respiratory insufficiency, the pulmonary pathology varies with the duration of the process.[15] Patients dying within the first 2 weeks show heavy lungs, usually more than 2000 g for the combined weight. They are uniformly consolidated, and the pleura usually is smooth and shiny. On cut section, they are airless and pale gray, frequently with a slimy consistency. Hemorrhagic foci and cystic changes secondary to assisted ventilation are seen.

Microscopically, there is extensive filling of alveoli, with proteinaceous exudate and changes of diffuse alveolar damage (DAD) secondary to oxygen toxicity. Patients dying within 1 week on the respirator have the exudative stage of DAD, including hyaline membranes with reactive atypical alveolar lining cells. In patients surviving more than 1 week, the changes of proliferative DAD have taken place, including intraalveolar fibroblastic proliferation extending into alveolar ducts and bronchioli (bronchiolitis obliterans). The marked reduction in the amount of *P. carinii* exudates and in the numbers of stainable cysts presumably are the result of treatment. Associated infections can be seen, particularly cytomegalovirus (CMV), other fungi such as cryptococcosis, and atypical mycobacteria. In patients with a less severe presentation, PCP frequently responds to treatment only to reappear one or more times in the following months or years. Many of these patients die of other causes.

Atypical manifestations of PCP may pose diagnostic challenges to clinicians and pathologists alike. Interstitial lung disease with exudative and proliferative DAD and with or without bronchiolitis obliterans may occur in the absence of oxygen toxicity.[16] Microscopic evidence of interstitial fibrosis can be seen, but the picture of a honeycomb lung is almost never seen, partly because patients do not survive long enough for such change to take place.

P. carinii may produce tissue necrosis, resulting in the formation of cavities (Fig. 45-5). If the cavities abut the pleura, pneumo-

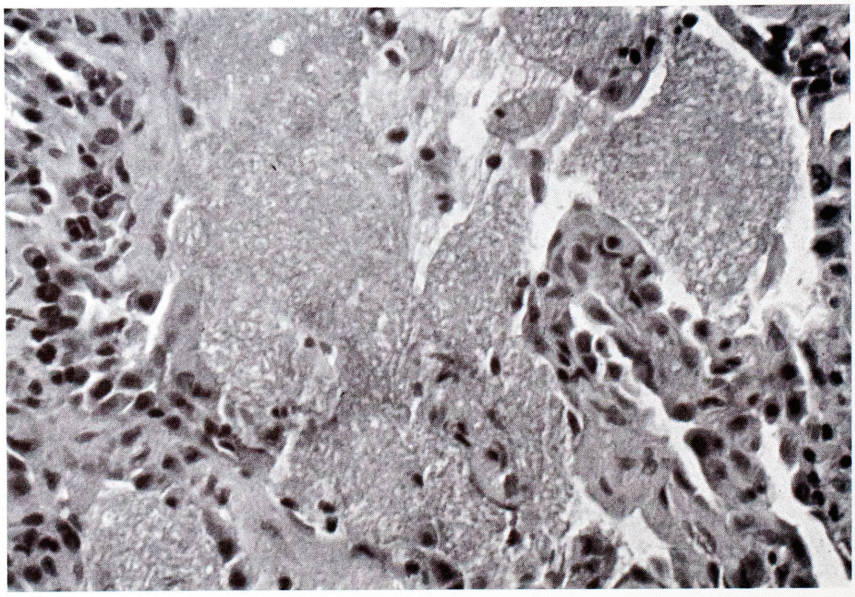

FIGURE 45-3. The alveolar spaces in *Pneumocystis carinii* pneumonia are filled with a pink, foamy exudate. There are increased numbers of lymphocytes in the alveolar walls; this finding is rare in adults but relatively common in children. (H & E stain; intermediate magnification.)

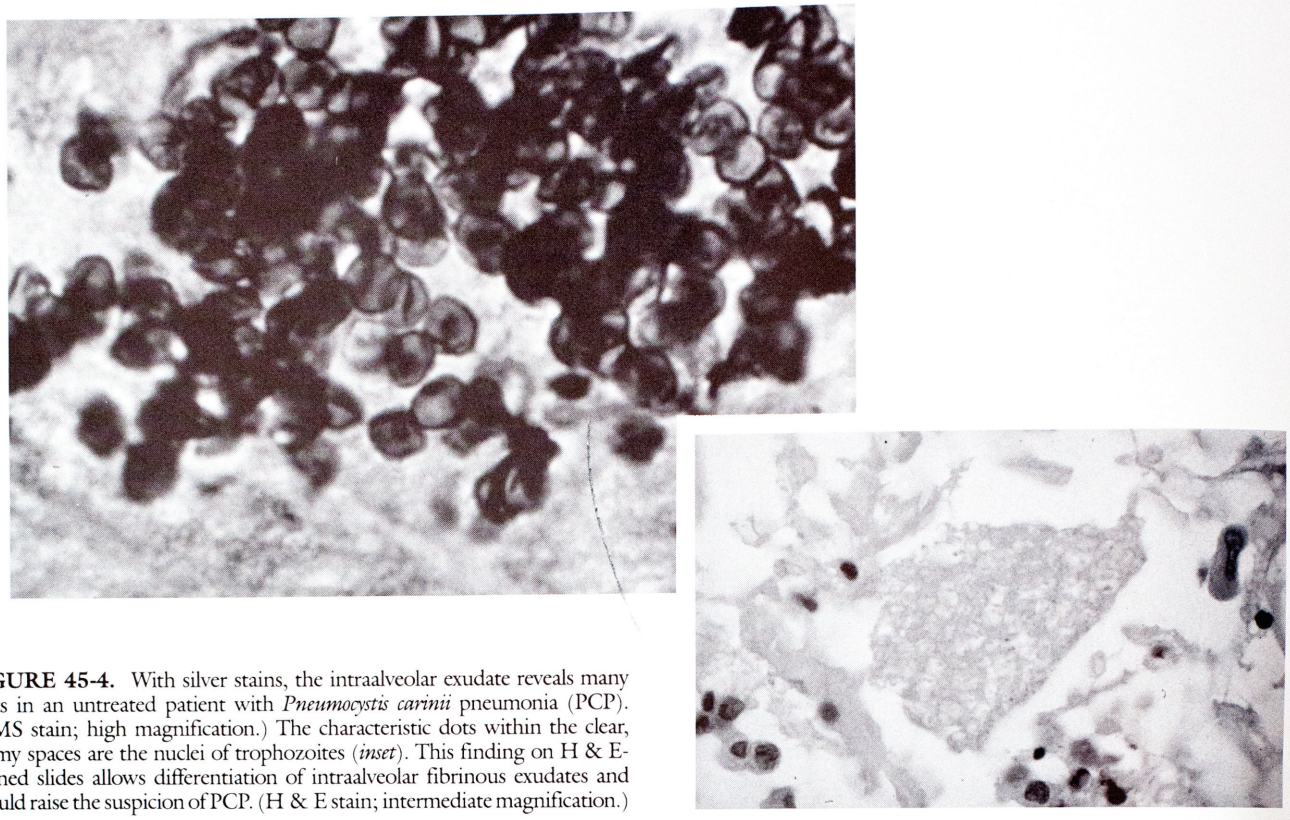

FIGURE 45-4. With silver stains, the intraalveolar exudate reveals many cysts in an untreated patient with *Pneumocystis carinii* pneumonia (PCP). (GMS stain; high magnification.) The characteristic dots within the clear, foamy spaces are the nuclei of trophozoites (*inset*). This finding on H & E-stained slides allows differentiation of intraalveolar fibrinous exudates and should raise the suspicion of PCP. (H & E stain; intermediate magnification.)

thorax may occur; margination of *P. carinii* colonies near the subpleural region can penetrate the pleura, forming a bronchopleural fistula with pneumothorax or hemothorax. The mechanisms of cavitation in PCP are not fully understood, but there is no doubt that tissue invasion and distention of the interstitial compartment of the lung plays a major role.[16, 16a] The change can be massive enough to reduce the volume of the alveoli to near collapse (Fig. 45-6). The collections of *P. carinii* in the interstitium undergo degeneration, calcification, and granuloma formation, eventually breaking down in areas of cavitation. We have observed that interstitial invasion by *P. carinii* around bronchioles may lead to their collapse and distention of distal air sacs by a valvelike mechanism and to cyst formation at the alveolar level.

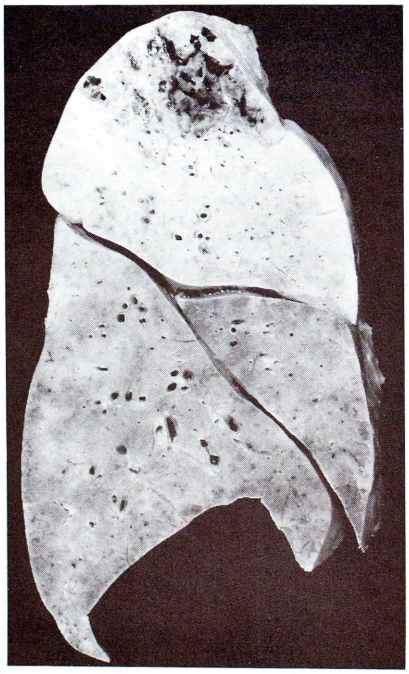

FIGURE 45-5. Cavitation occurred in a patient with untreated *Pneumocystis carinii* pneumonia (PCP) involving preferentially the right upper lobe. The hemorrhage is caused by cavitation; the mottled appearance of the remainder of the right upper and lower lobes is caused by PCP.

Within the pulmonary interstitium, it is easy for the *P. carinii* masses to dissect, for extended segments, the walls of pulmonary vessels, particularly veins, narrowing their lumens (Fig. 45-7). True vasculitis has been reported, but it is rare.[17] Luminal narrowing by *P. carinii* is probably not a main determinant of cavitation in PCP.[16a] Scattered foci of dystrophic microcalcifications are usually seen at the periphery of the cavities and may persist even after the disease has been cured.

P. carinii may produce a significant lymphoplasmacytic interstitial infiltrate that is more striking in children than adults. Because of this feature, the disease was originally called lymphoid interstitial pneumonia (LIP) in 1952.[6] The same designation was used in 1966 by Liebow and Carrington to describe adult patients in a totally different context.[18] Ironically, a true form of pneumonia with this name has become recognized as a major pulmonary process in people with AIDS, but it is not associated with PCP.[19]

Granulomatous responses vary from isolated scattered giant cells to discrete sarcoidlike granulomas that replace alveolar tissue. Caseating granulomas with peripheral palisading of histiocytes can be seen (Color Fig. 45-1).[20]

P. carinii infection, usually from a pulmonary focus, may disseminate to extrapulmonary sites. Preferred locations include

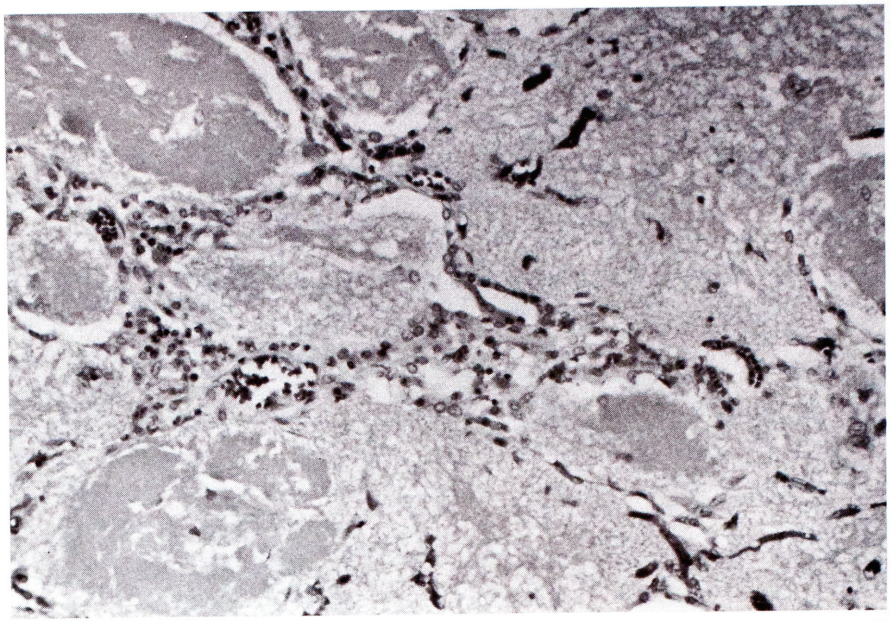

FIGURE 45-6. Interstitial invasion by *Pneumocystis carinii* of lung tissue adjacent to a cavitary lesion. Alveolar spaces are indicated by dense masses of fibrinous exudate. The foamy exudates distending the pulmonary interstitium are composed by trophozoites with lesser numbers of cysts. (H & E stain; low magnification.)

regional lymph nodes, liver, spleen, and bone marrow. Unusual sites include the hard palate, heart (*e.g.*, pericardium, myocardium of left ventricle, epicardial veins), thymic capsule, thyroid, eye, external auditory canal, intestine, and skin.[16] A patient with a case of hematogenous transplacental spread has been described.[21] The presence of *P. carinii* organisms in Virchow-Robin spaces of the brain cortex has also been reported.[22] In organs and locations other than the lung, *P. carinii* produces the same eosinophilic honeycomb exudates characteristic of the disease.

Toxoplasmosis

Toxoplasma gondii affects several organs selectively in immunodeficient patients and appears as a systemic disease only rarely. In the lungs, toxoplasmosis produces necrotizing lesions (Fig. 45-8). Definitive diagnosis requires demonstration of the characteristic tachyzoites or cysts in bronchial mucosa, intraalveolar exudates, areas of vasculitis, coagulative necrosis, and at the periphery of the lesions.[23] Pneumothorax has been rarely reported.[24] In some patients, the pneumonia can be lethal.[25] *T. gondii* can cause necrotizing encephalitis, which is the most common cause of focal brain lesions in patients with AIDS, and cause myocarditis, retinochoroiditis, meningitis, gastritis, enteritis, or orchitis.

Cryptosporidiosis

Infection by various species of *Cryptosporidium* usually produces a chronic diarrheal syndrome in severely malnourished and in immunosuppressed patients. Pulmonary involvement was first reported by Forgacs and colleagues in 1983.[26] In 1984, Brady and associates described a 32-year-old bisexual man with AIDS who had a history of chronic diarrhea and vomiting secondary to gastrointestinal cryptosporidiosis.[27] The patient developed respiratory symptoms and bilateral, diffuse interstitial pulmonary infil-

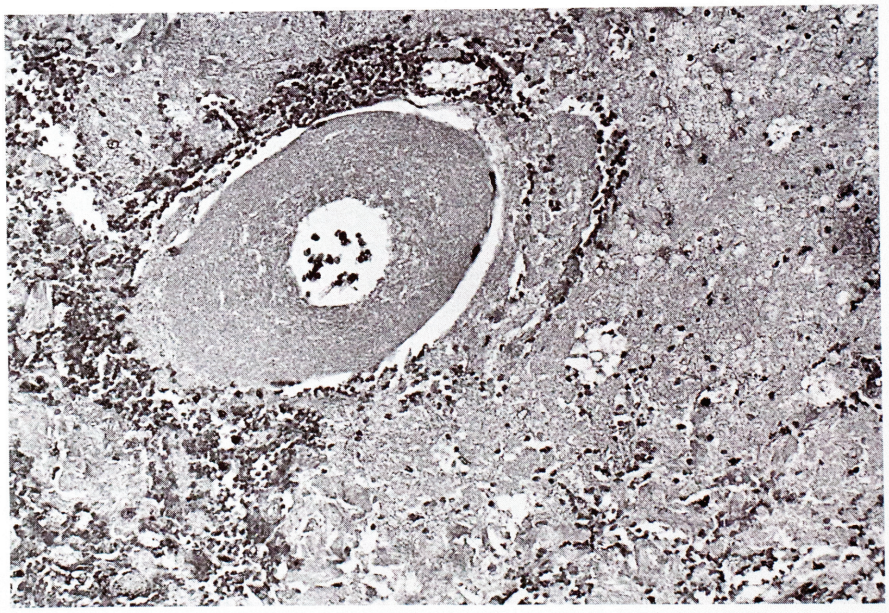

FIGURE 45-7. A peculiar medial dissection of a vein by *Pneumocystis carinii* exudate was found in a patient with cavitary *P. carinii* pneumonia shown in Figure 45-6. The *P. carinii* organisms produce massive distention of the interstitium. (H & E stain; low magnification.)

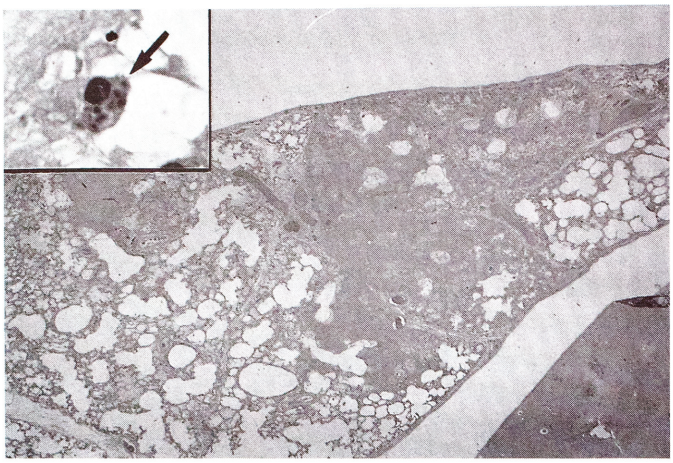

FIGURE 45-8. A patchy necrotizing pneumonia is characteristic of toxoplasmosis. (H & E stain; low magnification.) A cell contains the tachyzoites of the organism (*inset*). (H & E stain; high magnification.)

trates. Open lung biopsy revealed a severe interstitial pneumonitis and cryptosporidian trophozoites, best seen by acid-fast stain Kinyoun stain in the alveolar exudates.

In their review of 1990, Travis and colleagues observed that only six cases of respiratory cryptosporidiosis had been reported in the literature and added one case of their own.[28] Their review supports the view that respiratory cryptosporidiosis is characterized by chronic tracheitis, bronchitis, and bronchiolitis, which by itself does not cause severe pulmonary dysfunction. Pulmonary death usually results from the combined effects of cryptosporidiosis with other infections, such as those caused by *P. carinii*, CMV, and atypical mycobacteria.

Current and Garcia, in their review of 1991, reported that the number of cases of pulmonary cryptosporidiosis was growing rapidly.[29] They observed that diarrhea had not been reported in all of these patients. *Cryptosporidium* organisms can be recognized in sputum, tracheal aspirates, bronchoalveolar lavage fluid, brush biopsy specimens, alveolar touch preparations of biopsies, and the biopsy specimen itself (Color Fig. 45-2). Most patients with severe immunodeficiencies and *Cryptosporidium* sp. in their respiratory tract do not recover.

Microsporidiosis

Microsporida are obligate intracellular protozoan parasites increasingly seen in patients with AIDS.[30] AIDS-related microsporidiosis was first reported in the small intestine in 1983, and the species *Enterocytozoon bieneusi* was named and characterized in 1985.

Encephalitozoon hellem sp. nov. is a microsporidian capable of infecting epithelial cells of conjunctival, nasal, sinopharyngeal, and tracheobronchial mucosa.[31] The spores have an extrusion apparatus consisting of a coiled polar filament with an anchoring disk containing the sporoplasm or infective agent. After the obligate intracellular habitat is reached in a new host, the coiled polar filament is extruded to form a hollow tube through which the sporoplasm is inoculated into a host cell. We have seen a patient with microsporidan organisms of the urinary bladder and within macrophages in concentrated urine. Later at autopsy, extensive involvement of the kidneys, ureters, and respiratory system was found.[32]

Microsporida can be easily overlooked in tissue biopsy specimens because of their small size (0.5–1.5 μm), but the diagnosis can be made on hematoxylin and eosin–stained preparations by finding single or small groups of organisms in macrophages and in the cytoplasm of epithelial cells (Color Fig. 45-3). Brown and Brenn preparations show diagnostic equatorial gram-positive bands. Periodic acid–Schiff preparations show diagnostic polar dots.

Amebiasis

There is no evidence indicating that infection by *Entamoeba histolytica* is more severe in AIDS patients than in the general population.[33–35] Nevertheless, severe disease can occur with free-living amebas.[36,37] Infection by amebas of the genus *Naegleria* (*e.g., Naegleria fowleri*) produces a form of meningoencephalitis in young, healthy persons having a history of exposure to contaminated water. No extracerebral involvement has been observed in these patients. However, various species of the genus *Acanthamoeba* (*e.g., Acanthamoeba culbertsoni, Acanthamoeba castellani*) cause a subacute to chronic granulomatous encephalitis in immunocompromised persons having no history of exposure to contaminated water. Pulmonary involvement can occur in these patients, and the lung and the skin are frequently the port of entry of the organisms. Little is known about the pulmonary pathology of this infection.

Strongyloidiasis

The threadworm *Strongyloides stercoralis* may produce severe hyperinfections in patients with AIDS.[38] Progressive internal recycling causes large numbers of adult worms and migratory larvae to accumulate, causing mechanical damage to the absorptive surface of the intestine. Migration of the larvae from the intestine to the lungs produces pneumonitis with cough, hemoptysis, and dyspnea. Death may be a consequence of respiratory failure, central nervous system damage, peritonitis due to a perforated bowel, or persistent bacteremia. Histopathologically, migrating larvae are found in bronchoalveolar and interstitial locations, eliciting an inflammatory reaction that may include lymphocytes, histiocytes, giant cells, plasma cells, neutrophils, and eosinophils (Fig. 45-9).

Cryptococcosis

Other than PCP, the most frequent fungal pneumonias seen in patients with HIV infection are caused by *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Aspergillus* species, and *Candida* species.

The ubiquitous *C. neoformans* is the fourth most common cause of disseminated disease in patients with AIDS. In these and other immunosuppressed patients, meningitis is the most common manifestation of the infection, but the lung may be concurrently involved (Fig. 45-10).[39,40] Meningitis and pneumonitis, pleural effusions, lymphadenitis, myocarditis, peritonitis, and retinitis may also occur in these patients (see Chap. 43).[41]

Histoplasmosis

Disseminated histoplasmosis occurs in patients with AIDS as a result of a primary event or after reactivation of a previous infection.[42] In the United States, the number of AIDS patients with

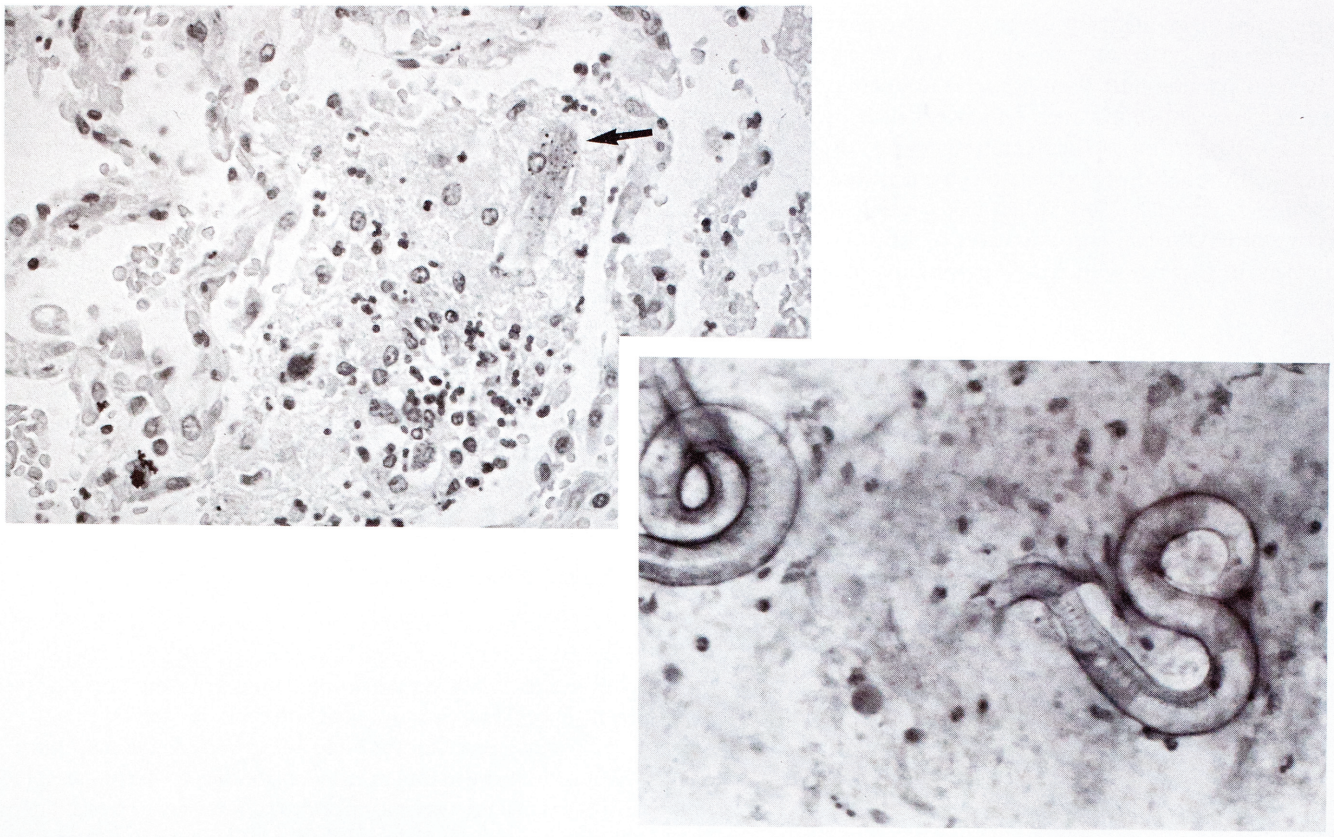

FIGURE 45-9. A larva of *Strongyloides stercoralis* (*arrow*) is seen in a patient with acquired immunodeficiency syndrome and hyperinfection. (H & E stain; intermediate magnification.) The parasite may be identified in bronchial washings (*inset*). (Lugol solution; high magnification.)

histoplasmosis is higher in areas where histoplasmosis is endemic (*e.g.*, Ohio, Missouri, or Mississippi River valleys).[43] After a primary pulmonary infection, lymphohematogenous dissemination may produce lesions at distant sites, including bone marrow, liver, spleen, lymph nodes, adrenal, retina, choroid, and brain. Diagnosis is made by the identification of the characteristic budding yeasts in tissues. Extracellular and intracellular yeasts may be observed on smears of peripheral blood from AIDS patients with disseminated disease.

Coccidioidomycosis

Disseminated coccidioidomycosis has been reported in patients with AIDS.[44,45] After the inhalation of airborne arthrospores, a

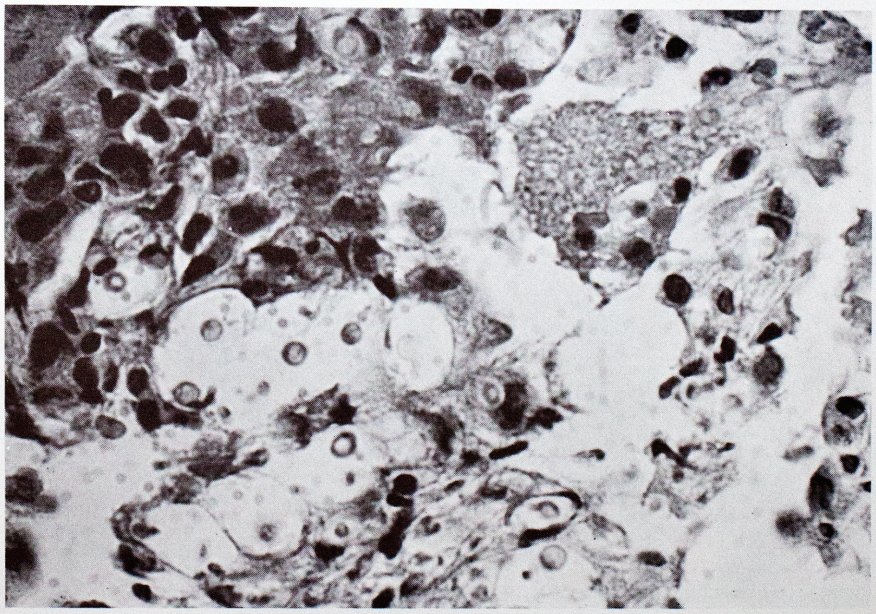

FIGURE 45-10. Combined cryptococcal infection and *Pneumocystis carinii* pneumonia. (H & E stain; high magnification.)

primary pulmonary infection develops. The organisms disseminate to extrapulmonary sites through blood vessels and lymphatics. Besides pneumonitis with bilateral nodular infiltrates, patients may present with meningoencephalitis, subcutaneous abscesses, osteomyelitis, arthritis, tenosynovitis, thyroiditis, and prostatitis. Although histologic involvement of the liver, spleen, lymph nodes, adrenals, and kidneys occur, infections of these organs are often clinically silent. Because of the profound immune impairment in patients with AIDS, granulomas may not be well formed.

Aspergillosis

Aspergillosis occurs rarely in patients with AIDS. In the study by Denning and colleagues of patients with HIV infection and pulmonary aspergillosis, 10 of 13 patients had invasive aspergillosis.[46] Three patients had a peculiar form of the disease, which the researchers designated "obstructive bronchial aspergillosis."[46] These patients were much sicker and required supplemental oxygen for severe dyspnea. The chest roentgenograms revealed diffuse bilateral infiltrates involving the lower lobes. Fungal casts and aspergillomas were identified in the airways. In one patient in this study and two patients elsewhere, extensive exudates, designated pseudomembranes, containing aspergilli lined the tracheobronchial tree.[47,48]

Candidiasis

Mucosal oroesophageal candidiasis is a common occurrence in patients with AIDS; much less frequently, *C. albicans* produces pneumonia with abscess formation (Color Fig. 45-4) and with the characteristic budding yeasts and pseudohyphae (Fig. 45-11).[49]

VIRAL, MYCOPLASMAL, AND CHLAMYDIAL INFECTIONS

Cytomegalovirus

CMV is a major pathogen in patients with AIDS.[50,51] More than 90% of homosexual men have antibodies to CMV, and in one study, 30% excreted CMV in their urine.[50] It seems probable that sexually active homosexual men are regularly exposed to CMV and may be repeatedly reinfected. AIDS patients also readily excrete CMV in their throats and have persistent viremia.

In Africa, this infection is relatively rare, but CMV is diagnosed in about two thirds of all autopsies of HIV-infected patients in the United States. Second only to the adrenal, the lung is commonly infected by CMV. Infection results in focal or severe diffuse interstitial and hemorrhagic pneumonia. It can be extremely severe and produce overwhelming pulmonary insufficiency, often as the terminal event.

Diagnosis in tissues is frequently established by identification of characteristic viral inclusions in endothelial and epithelial cells. The alveolar lining cells may show few or many cells with intranuclear and coarse intracytoplasmic inclusions. Diagnostic methods include DNA *in situ* hybridization, cytology, immunoperoxidase, and immunofluorescence (see Chap. 42).

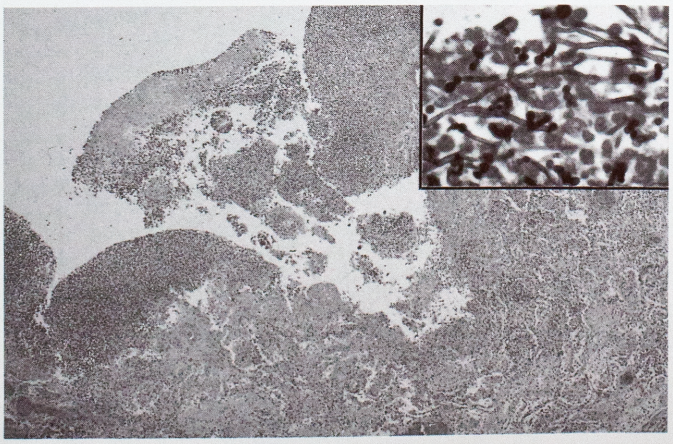

FIGURE 45-11. Necrotizing bronchiolitis with microabscesses in *Candida albicans* infection. (H & E stain; low magnification.) Stained fungi (*inset*). (GMS stain; intermediate magnification.)

Herpesvirus

In HIV-infected patients, herpes simplex virus causes extensive mucocutaneous disease and esophagitis, tracheitis, bronchitis, and pneumonia.[52] AIDS patients have more frequent and more serious recurrences, but disseminated infection is rare.

Disease reactivation is to be expected, because more than 90% of homosexual men have antibodies to herpes simplex type 2. Interstitial pneumonic episodes can be part of a primary herpes simplex viremia, but only a few cases have been reported (Color Fig. 45-5). Early recognition and treatment may improve outcome, and prophylaxis with acyclovir may reduce the frequency of recurrences.[53–55]

Adenovirus

Adenoviruses may cause bronchopulmonary infection, and types 4 and 7 have been associated with pneumonia.[56,57] Adenoviral syndromes in immunocompromised patients are probably the result of reactivation of latent viral infections.[58] Radiographs show patchy interstitial infiltrates, primarily of the lower fields. Adenoviral infection may be associated with other opportunistic agents, such as CMV and *P. carinii*. No specific antiviral therapy is available and AIDS patients with adenovirus pneumonia do not recover the way many immunocompetent patients do.

Mycoplasma

Incidence of *Mycoplasma pneumoniae* infection in the immunodeficient population is unknown, and descriptions of this condition in AIDS patients have been purely anecdotal in our experience. However, a novel pathogenic mycoplasma tentatively called *M. fermentans, incognitus* strain, was demonstrated in necrotizing lesions of the lung and other organs of 22 AIDS patients and 6 non-AIDS patients who died of an acute flulike illness.[59] The infection produces severe interstitial pneumonitis with acute respiratory distress syndrome. *M. fermentans incognitus* has been demonstrated by immunochemistry using monoclonal antibodies (Color Fig. 45-6) and by electron microscopy.[60] The spherical *Mycoplasma* organisms are 140 to 280 nm in diameter, have a well-defined outer limiting membrane, and are often seen in the cytoplasm of degenerating cells.

Chlamydia

Chlamydia pneumoniae, TWAR strain, an important respiratory pathogen, has been associated with mild epidemics. The incidence among HIV-infected patients is still undetermined.[61,62]

BACTERIAL INFECTIONS

Tuberculosis

A full treatment of tuberculosis is provided in Chapter 41. About 4% of patients with tuberculosis appear in the AIDS registries in the United States, but in Africa, tuberculosis is frequently disseminated and is seen in almost one third of all AIDS patients at autopsy.[63,64] About one half of these patients had reactivations of previous infections, which often represents an early manifestation of deepening immunodeficiency. Cavitation appears to be unusual, but intrathoracic lymphadenopathy occurs frequently. Extrapulmonary and disseminated forms of tuberculosis are the most difficult to diagnose and have the highest mortality. Radiographic studies are atypical, and sputum smears are less sensitive. The diagnosis depends greatly on the examiner's awareness. In European and South American series, most of the HIV-infected patients with tuberculosis are drug addicts with extrapulmonary or disseminated forms.[65]

The histologic pattern of tuberculosis varies with the patient's immune status from granulomatous to anergic. As the numbers of CD4 lymphocytes decrease, the Langhans cells decrease, and the numbers of *Mycobacterium tuberculosis* bacilli increase. The granulomas gradually become less well defined, and the pattern of necrosis changes from caseous to mixed caseous plus suppurative and then to suppurative. In the early stages of HIV infection, tuberculosis is caseogranulomatous, paucibacillary, and reactive; in the terminal stages, tuberculosis is miliary or suppurative, multibacillary, and anergic. Tuberculosis preferentially involves lower lobes and frequently appears as a diffuse infiltrative process. Treatment is with rifampin, isoniazid, and ethambutol, but drug resistance is on the rise.[66]

Using DNA fingerprinting to identify different strains of the tuberculosis bacterium, Small and colleagues demonstrated that four AIDS patients had become infected with a new, multidrug-resistant form of the disease while undergoing treatment for a previously diagnosed tuberculosis infection.[66a] All four patients died of the effects of the second tuberculosis infection after almost recovering from the first. Typically, drug-resistant strains of *M. tuberculosis* arise because of inadequate or incomplete drug therapy. Small's study indicates that reinfection is a third possible explanation for the emergence of drug-resistant tuberculosis.

Mycobacterium avium-intracellulare

Except for the *Mycobacterium avium-intracellulare* complex (MAI), infections due to nontuberculous mycobacteriosis are uncommon, but some may be significant in patients with AIDS.[67] In a study of positive sputum cultures for *Mycobacterium gordonae*, for example, only the HIV-seropositive patients had respiratory tract infections.[68] Another report indicated that *Mycobacterium kansasii* can be a cause of diffuse pulmonary disease.[69] Other mycobacteria rarely capable of producing disease include *Mycobacterium asiaticum*, *Mycobacterium flavescens*, *Mycobacterium malmoense*, *Mycobacterium scrofulaceum*, *Mycobacterium szulgai*, *Mycobacterium xenopi*, and *Mycobacterium bovis*.[70]

MAI is the third most common infectious agent found in HIV-infected patients who develop pulmonary abnormalities. It is an ubiquitous environmental saprophyte that, until the advent of AIDS, rarely caused disseminated disease. Even patients with malignant neoplasms who developed atypical mycobacterial infections were usually infected by species other than MAI. However, disseminated disease affected more than 20% of the AIDS patients at the National Institutes of Health and more than 50% in other series.[71,72]

MAI tends to occur late in the course of HIV infection. The portal of entry is probably the gastrointestinal tract. Patients with disseminated infections present with fever, weight loss, and debilitation. MAI is usually found in the lung, lymph nodes, spleen, liver, bone marrow, and intestine. Special stains (*e.g.*, Ziehl-Neelsen) should be performed on all biopsy specimens from AIDS patients, even if granulomas are absent. Most AIDS patients with disseminated MAI are also mycobacteremic, and colony count quantification of blood cultures is a good parameter for assessing therapy (see Chap. 41).[73]

Usual and Unusual Pneumonia

The incidence of usual and unusual (*i.e.*, pyogenic) bacterial pneumonias in HIV-infected patients varies from institution to institution, but the potential risk for the immunodeficient population is great.[74] Most bacteria enter the respiratory tract by aspiration of oral secretions or hematogenously. The most common pathogens are the encapsulated organisms *Haemophilus influenza* and *Streptococcus pneumoniae*, which may cause, particularly in children with AIDS, significant bacteremia and multilobar pneumonia. Less common pathogens include group B streptococci, *Bordetella bronchiseptica, Branhamella catarrhalis, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae, Salmonella enteritidis, Staphylococcus aureus*, and *Legionella pneumophila*.

Bacillary Angiomatosis

Bacillary necroepithelioid angiomatosis is a transitional term for an emerging systemic infection caused by pleomorphic bacilliform microorganisms (*i.e.*, biotype *Rochalimaea henselae* sp. nov.). These are classified under the purple eubacterial alpha-2 subgroup of the class Proteobacteria.

We have studied more than 100 HIV-infected patients who also had a diagnosis of bacillary angiomatosis/cat-scratch disease complex. Only four of these patients had pulmonary involvement. All were unsuspected clinically. The infecting microorganisms enter the human host through injured epidermal or mucosal surfaces and the inoculating mechanisms include cat bites and scratches, which are the most frequent vectors; dog bites; punctures by wood splinters, thorns, porcupine quills; direct transfer through hangnails from the soil of tropical plants; and, anecdotally, paper cuts. There is often no history of injury.

After initial multiplication at the portal of entry, groups of bacilli spread to the lymph nodes and abdominal and thoracic viscera, including lungs, where they multiply. Occasionally, they return to the skin and cause foci of secondary infection (*i.e.*, crops of cutaneous papules). In addition to the larynx and lung, involvement of the skin, heart, stomach, intestine, liver, kidney, lymph

nodes, spleen, bone, bone marrow, adrenal, and choroid plexus have been described.[75–79]

In the lung and other organs, there may be colonies of entangled argyrophilic bacilliform microorganisms (*i.e.*, granular clouds) in areas of miliary necrobiosis in connective tissue (Fig. 45-12).[80] The bacteria are mostly extracellular, usually present in the tissue between neovascular spaces, and are 1.0 to 3.0 μm long and 0.1 μm in diameter. Karyorrhectic and pyknotic granulocytes, epithelioid macrophages, reactive vessels proliferating around these areas, and hyalinoid repair of necrotic tissue are also characteristic.

Nocardiosis

Patients with AIDS may develop disseminated nocardial infections.[81] The bacteria may be isolated from blood cultures. Infection begins in the lung; it may be acute, subacute, or chronic. In addition to pneumonia and pleural effusion (*i.e.*, empyema), the clinical presentations include purulent pericarditis, retropharyngeal abscess, subcutaneous abscesses, draining sinus tracts, brain abscesses, and cervical osteomyelitis.

Rhodococcosis

Rhodococcus equi, formerly referred to as *Corynebacterium equi*, produces pneumonia in animals and rarely in man. It is common in the soil of farms and livestock areas, and most human infections occur in immunocompromised patients.

R. equi produces cavitary pneumonias that are difficult to treat and that have protracted courses (Fig. 45-13). *R. equi* has been identified as an opportunistic pathogen in AIDS patients. Sierra and colleagues reported the case of an HIV positive 29-year-old female intravenous drug abuser who presented with systemic *R. equi* infection.[82] Empyema, renal abscess, and bloodstream involvement developed initially, with brain and subcutaneous skin abscess developing later. The course of her disease was so severe and relapses so numerous, despite all therapeutic attempts, that the physicians proposed that *R. equi* infections in HIV-positive patients should fulfill the criteria for AIDS. A handful of other cases of cavitary pneumonia in AIDS patients have been associated with *R. equi*, including an inflammatory pseudotumor of the lung.[83–85]

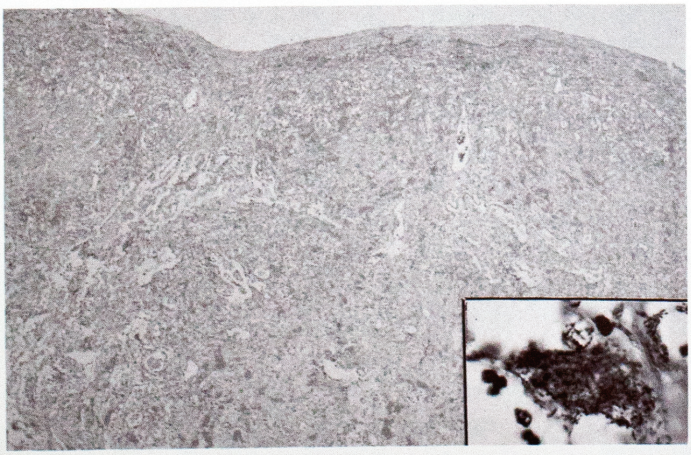

FIGURE 45-12. Pulmonary involvement in bacillary angiomatosis. (H & E stain; low magnification.) Stained organisms (*inset*). (Angritt-Wenger silver method; high magnification.)

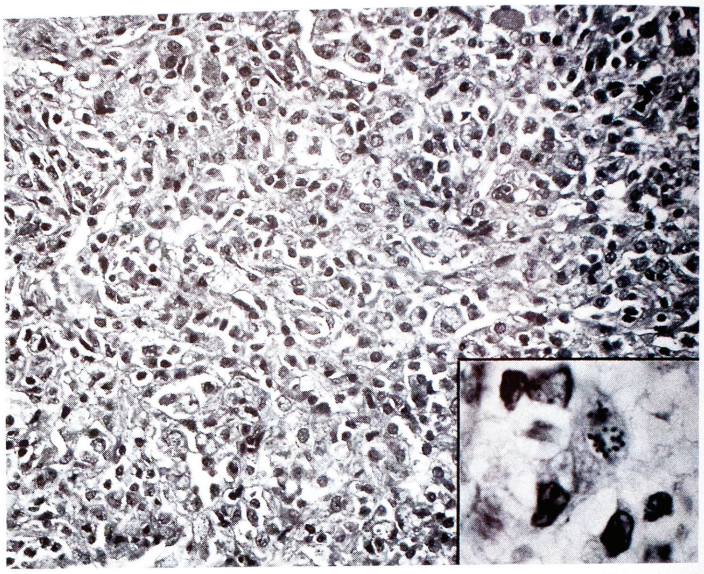

FIGURE 45-13. *Rhodococcus equi* pneumonia is characterized by dense lymphohistiocytic infiltrates. (H & E stain; intermediate magnification.) A histiocyte contains the organisms (*inset*). (Oil immersion view; courtesy of A.M. Marty, M.D., Washington, DC.)

Malakoplakia

Malakoplakia commonly occurs in the urinary bladder and is associated with *Escherichia coli* infection in more than 75% of patients with AIDS. The lungs are rarely involved, with less than 10 cases of pulmonary malakoplakia reported in the medical literature.

The lesions of malakoplakia may be somewhat nodular or circumscribed, and radiographically, they resemble carcinoma (Fig. 45-14). Histologically, malakoplakia represents exuberant granulomatous inflammation consisting of sheets of granular histiocytes with eccentric nuclei referred to as Von Hansemann cells. Admixed lymphocytes, neutrophils, and plasma cells may also be seen. Gray targetoid spherules, absolutely characteristic of the lesion, are seen in the cytoplasm of the histiocytes and are referred to as Michaelis-Guttman bodies. They are composed of a phospholysosomal core with peripheral mineralization by calcium, iron, and phosphate. Von Kossa stains for calcium are positive and differentiate these structures from the fungal organisms they resemble. Malakoplakia is thought to be caused by a defect in macrophage function that generates abnormal intracellular bactericidal killing or digestion.

In 1972, Gupta and associates described the first case of pulmonary involvement by malakoplakia occurring in a 61-year-old, severely debilitated woman.[86] She initially had malakoplakia of the urinary bladder with extensive involvement of the left kidney, which required nephrectomy. Postoperatively, she developed a gastrocutaneous fistula, had a complicated course, and died. At necropsy, friable tumorlike masses of malakoplakia were observed in the lower lobe bronchi in association with extensive patchy areas of bronchopneumonia that were also caused by malakoplakia. Lesions of malakoplakia resembling metastatic carcinoma were found in the lumbar vertebrae, the other kidney, and the gastrocutaneous fistula. The causative agents of the malakoplakia in this patient were *E. coli* and *Klebsiella* organisms.

In 1982, Colby and colleagues added two cases of pulmonary malakoplakia to the literature on immunosuppressed patients.[87] In

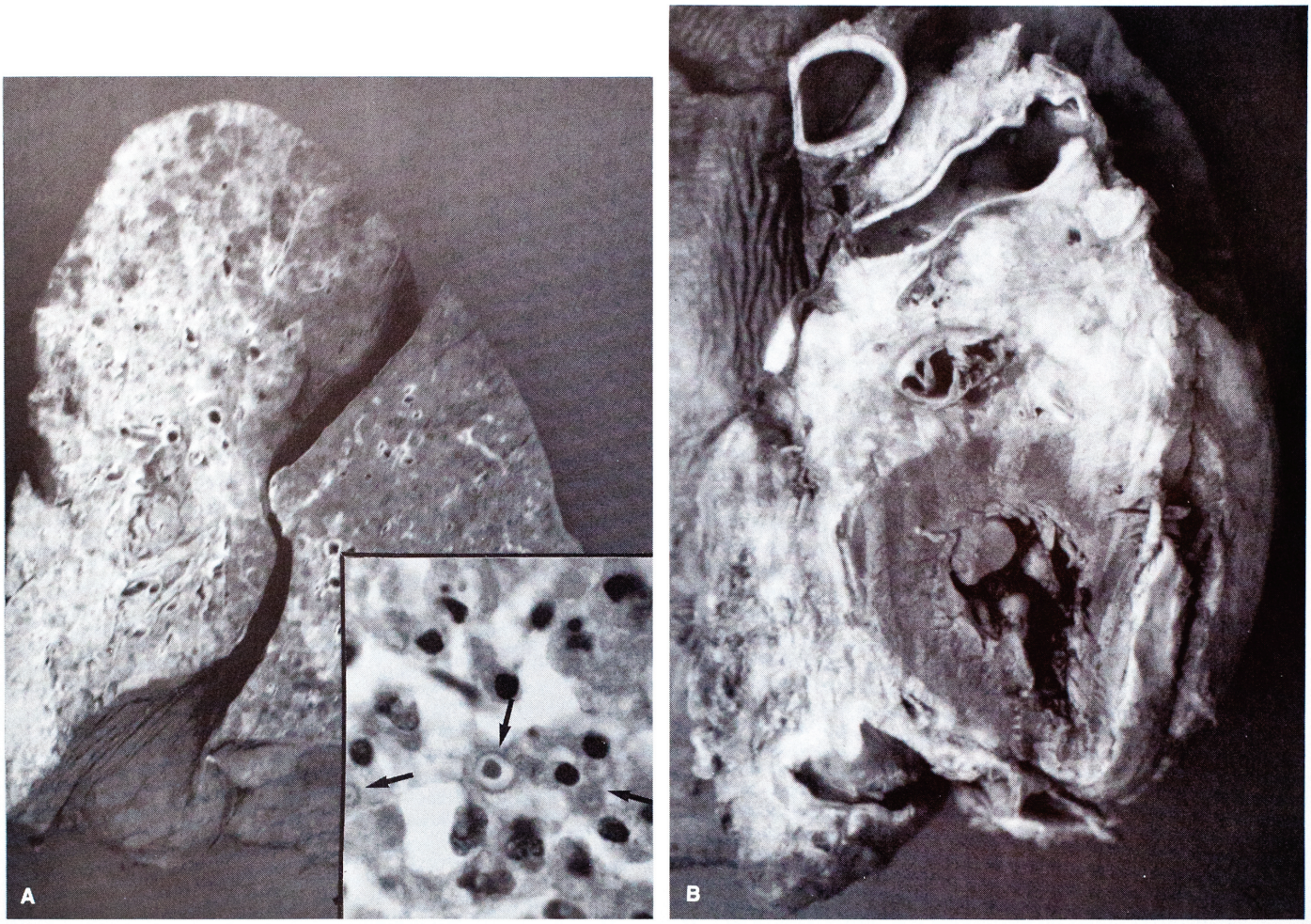

FIGURE 45-14. (**A**) Malakoplakia caused by *Rhodococcus equi* extensively involves the left lung in a middle-aged woman with acquired immunodeficiency syndrome. The characteristic histologic appearance includes histiocytes and Michaelis-Guttman bodies (*inset, arrows*). (H & E stain; high magnification.) (**B**) The process also encases the heart, simulating a tumor. (Courtesy of Paulina Ojeda, M.D., Bogota, Colombia.)

both instances, the causative organism was *R. equi*. Subsequent reports by research teams led by Crouch and Hodder detailed cases of systemic malakoplakia with cavitary lung lesions due to *E. coli*.[88,89] One patient had in addition a perianal mass due to malakoplakia. He was immunocompromised after a renal transplant, and all attempts to cure the perianal abscess and lung lesion were unsuccessful. However, after the dose of the patient's immunosuppressive therapy was reduced, the perianal and lung lesions resolved completely, and the bactericidal activity of the patient's neutrophils and macrophages returned to normal.

Two cases of pulmonary malakoplakia due to *R. equi* have been reported in patients with HIV infection. Scannell and colleagues described a male homosexual horse trainer with HIV infection and porphyria cutanea tarda who developed a progressive cavitary mass in the right upper lobe.[90] Resection of the lesion demonstrated characteristic features of malakoplakia. Schwartz and associates also described an HIV-positive homosexual man with a large cavitary lingular abscess due to *R. equi* and malakoplakia.[91] Why *R. equi* produces systemic abscesses in HIV-infected patients and malakoplakia in others is not apparent from the few reported cases.

OTHER PULMONARY PROCESSES

Lymphoid Interstitial Pneumonia

LIP was recognized before the AIDS epidemic, but most cases probably represented low-grade lymphocytic lymphomas with preferential pulmonary involvement and an indolent clinical course.[92] LIP is a common manifestation of HIV infection in children, and its presence establishes the diagnosis of AIDS. In adults, LIP is rarer and, for unknown reasons, occurs more often in patients of Haitian descent. Unlike children, LIP in adults does not justify a diagnosis of AIDS.[19]

Children with LIP have associated bacterial and viral infections, fail to thrive, and have parotiditis. Adults manifest symptoms of AIDS-related complex, often with concomitant bacterial and viral infections. The chest radiographs of children with LIP demonstrate bilateral reticulonodular infiltrates resembling miliary tuberculosis. In adults, there may be patchy areas of alveolar consolidation in addition to the miliary infiltrates. Dysgammaglobulinemia frequently develops in these patients.

Pathologically, the mildest or earliest forms of LIP represent

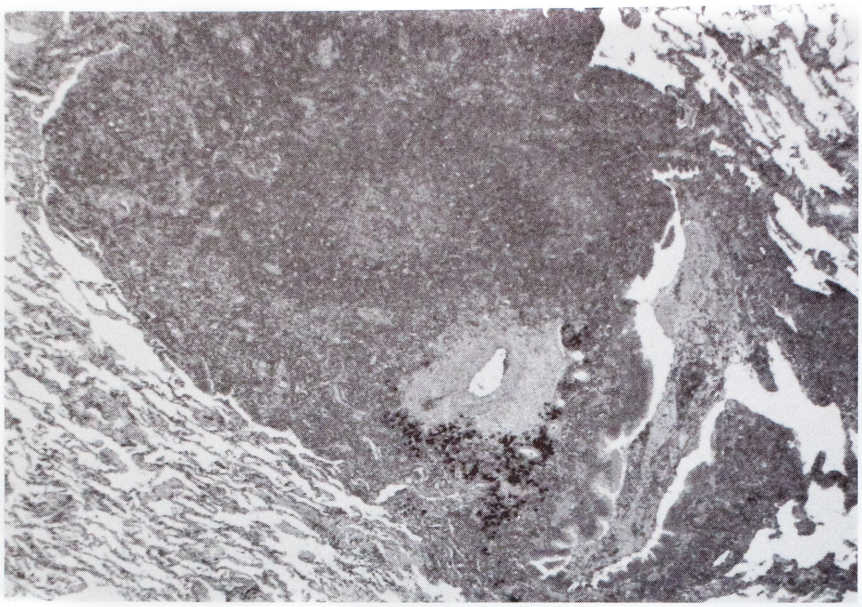

FIGURE 45-15. The proliferation of lymphocytes and expansion of bronchial-associated lymphoid tissue, including germinal centers, are seen in a 35-year-old Haitian man with acquired immunodeficiency syndrome and lymphoid interstitial pneumonia. (H & E stain; low magnification.)

hyperplasia of bronchial associated lymphoid tissue without interstitial involvement. Aggregates of lymphocytes and plasma cells form around airways and blood vessels (Figs. 45-15 and 45-16). As the disease progresses, they extend along the alveolar septa. In the later stages, confluent nodules as large as 2.5 cm in diameter form. The lung parenchyma in these areas is solid and resembles a lymph node. LIP has not progressed to interstitial fibrosis of the lung in children or adults; progression to Kaposi sarcoma has been observed in adults only.

LIP in children can be a debilitating disease, producing respiratory insufficiency with severe hypoxemia and digital clubbing. In adults, LIP is usually asymptomatic but produces radiographic features that mimic PCP. The pathogenesis of LIP is unclear but is probably caused by the direct effects of HIV on the lung.[93] The effects of Epstein-Barr virus (EBV) have also been proposed for the cause of LIP. However, in a large series of patients with LIP, two children with LIP had no serologic evidence of prior EBV infection.[19] Only one child had serologic evidence of acute EBV infection at the time of diagnosis of LIP, and *in situ* hybridization of the lung biopsy specimen for EBV showed a rare positive cell. These findings mitigate against EBV as the main cause of LIP, but EBV may be a cofactor in triggering the lymphoproliferative response seen in the lung and other organs in these patients.

Kaposi Sarcoma

As many as 45% of all HIV-infected homosexual men may present with or will develop Kaposi sarcoma at some point in the illness.[94] Although there is some evidence indicating that the incidence of Kaposi sarcoma is decreasing, it still remains the most common form of malignancy in these patients. Only 4% to 10% of heterosexual intravenous drug abusers and 8% to 12% of HIV-infected Haitian patients develop Kaposi sarcoma. The incidence is much lower among hemophiliacs (1%), children, and patients with no known risk factors.

There are four clinicoepidemiologic forms of Kaposi sar-

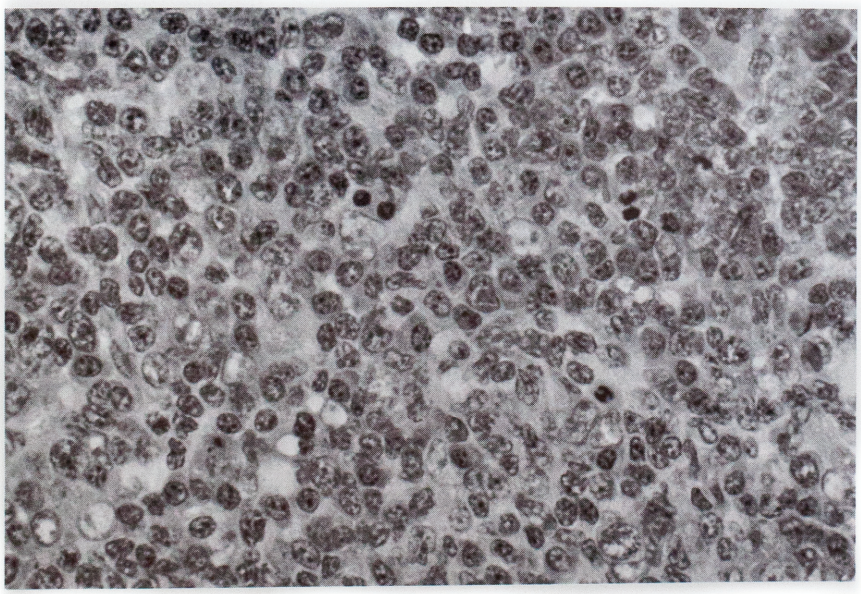

FIGURE 45-16. Dense cellular proliferation is present in a child with acquired immunodeficiency syndrome and lymphoid interstitial pneumonia. (H & E stain, intermediate magnification.)

coma: classic Kaposi sarcoma, which affects elderly men of Mediterranean or Ashkenazic Jewish origin in the west; endemic Kaposi sarcoma, which occurs in Central Africa and represents approximately 10% of all neoplasms in places such as Kenya, Tanzania, and Zaire; iatrogenic Kaposi sarcoma which occurs in immunosuppressed patients treated with corticosteroids, azathioprine, or cyclophosphamide (particularly after organ transplants); and epidemic Kaposi sarcoma, which is associated with HIV infection.[95]

The epidemic Kaposi sarcoma of AIDS is characterized by the sudden occurrence of widely disseminated lesions of the skin, oral mucosa, pharynx, lymph nodes, and visceral organs, such as the gastrointestinal tract, lung, liver, and spleen. The onset of pulmonary Kaposi sarcoma is an ominous sign and is often the terminal event. Fewer than 20% of patients survive more than 2 years. Only 5% of patients have visceral involvement without skin lesions. Common sites of involvement are the face, occipital region behind the earlobes, oropharynx, and palate. Rare locations include the central nervous system and testes.

Pulmonary Kaposi sarcoma may arise as a primary pulmonary disease but much more frequently as part of a systemic process. It occurs in as many as 20% to 25% of patients with cutaneous involvement. Clinically and radiographically, when unassociated with skin lesions, Kaposi sarcoma of the lung is indistinguishable from opportunistic infections. Most patients present with some combination of cough, dyspnea, fever, hemoptysis, and stridor. Pleural effusion is common and hemorrhagic in character; pneumothorax rarely has been reported.

Pathologically, Kaposi sarcoma involves the lung parenchyma, the mucosa of the tracheobronchial tree, and the pleura. The parenchymal lesions frequently consist of diffuse confluent patchy areas of red hemorrhagic consolidation (Fig. 45-17). Other lesions appear brown. A preferential linear involvement of lymphatic pathways along bronchovascular bundles and veins at the interlobular septa is also characteristic. Endobronchial lesions of Kaposi sarcoma are well recognized by bronchoscopy and highly characteristic; they are erythematous to violaceous and tend to be prominent at the orifices of segmental bronchi in a circumferential manner. In patients with Kaposi sarcoma of the skin, biopsies of the bronchial lesions are discouraged because of the threat of hemorrhage.

Histologically, the lesions of Kaposi sarcoma show a dense, predominantly spindle cell component with interlacing fascicles surrounding endothelial-lined vascular channels (Fig. 45-18). This classic microscopic appearance alternates with others having telangiectatic features or a prominent lymphoplasmacytic cellular infiltrate, called inflammatory Kaposi sarcoma. Hemosiderin deposits and hyaline globules within the spindle cells are also characteristic. The nuclear and cytologic atypia may be mild, and few mitoses may render the diagnosis difficult for some patients; many of these cases, particularly the small biopsies, may be labeled "fibrosis."

Because of the peculiar gross and microscopic features of the lesion and because of its biologic behavior of regression, spontaneously or on withdrawal of immunosuppressive therapy, the neoplastic character of Kaposi sarcoma has been questioned. Fukunaga and Silverberg showed that the lesions exhibit DNA diploidy and that the S-phase fraction is usually low (mean, 6.9%).[96] Based on their findings and previously reported evidence, they suggest that Kaposi sarcoma is probably a proliferative process of a nonmalignant character. The relation between Kaposi sarcoma and CMV has also been the matter of some debate. The presence of CMV has been observed by immunohistochemistry and *in situ* hybridization, suggesting an association between this virus and Kaposi sarcoma.[97] Human papilloma virus-16 DNA sequences have also been demonstrated in Kaposi sarcoma.[97a]

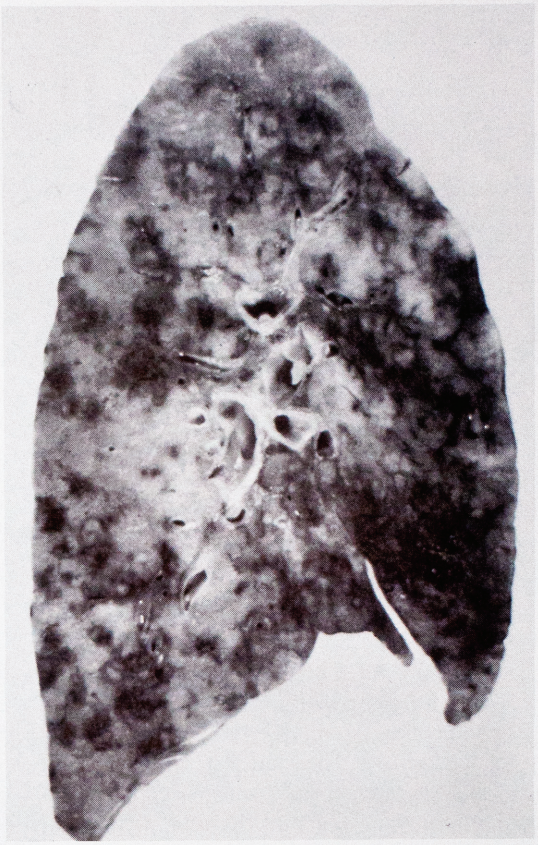

FIGURE 45-17. Massive involvement of pulmonary tissue in a middle-aged patient with acquired immunodeficiency syndrome and Kaposi sarcoma. (From Saldana MJ. Localized diseases of the bronchi and lungs. In: Silverberg SG, ed. Principles and practice of surgical pathology. Vol. 1. New York: Churchill-Livingstone, 1990:744.)

Pulmonary Lymphomas

Non-Hodgkin lymphoma (NHL) is the second most common malignancy associated with HIV infection, occurring in approximately 5% to 10% of patients. Most patients present with involvement of extranodal sites, primarily the central nervous system, gastrointestinal tract, and bone marrow. In a study by Raphael and colleagues, only 3 (2.7%) of 113 patients had pulmonary involvement as the initial manifestation of their lymphoma.[98] In a comparable study by Knowles and associates, only 1 (1.1%) of 89 patients had lung lymphoma.[99] Sider and colleagues found a significantly higher incidence (31%) of thoracic involvement in AIDS-related lymphoma (ARL), which included such well-known sites of origin as the heart and blood vessels, mediastinal contents, and chest wall.[100] They also found that ARL involving the lungs frequently presented with pleural effusion and interstitial lung disease. Hilar and mediastinal lymphadenopathy occurred infrequently. Zompatori and associates reported a higher

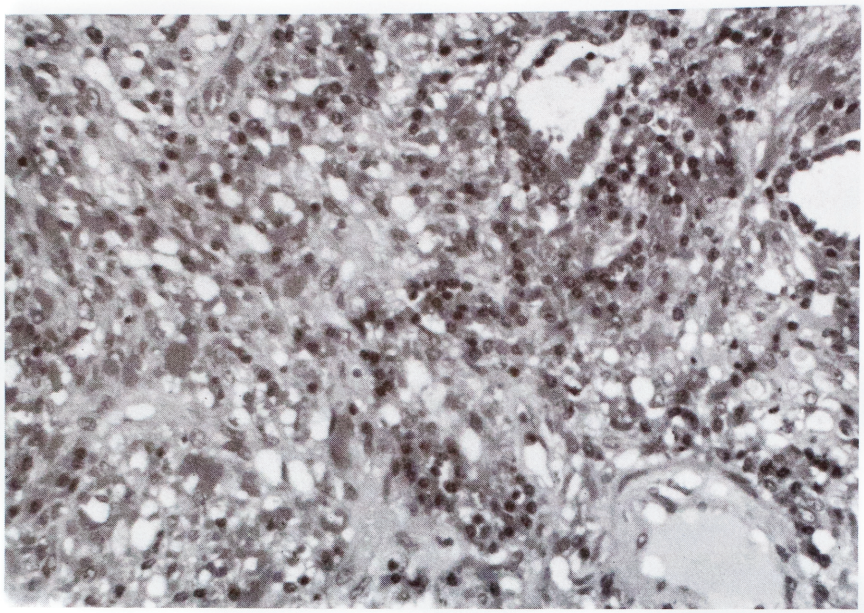

FIGURE 45-18. The characteristic spindle cell and hemorrhagic proliferation of Kaposi sarcoma involves the lung in the same patient as in Figure 45-15. The darker areas (*right*) represent lymphoid interstitial pneumonia. (H & E stain; intermediate magnification.)

incidence (25%) of ARL with bilateral multinodular lung disease and a tendency for chest wall invasion.[101]

Polish and colleagues reported four cases of ARL with pulmonary involvement.[102] The clinical findings were nonspecific and included fever, weight loss, generalized lymphadenopathy, chest pain, and cough. Three of the four patients died 4 to 5 months after diagnosis.

Almost invariably, these lymphomas are B-cell large cell tumors of intermediate or high grades. They are frequently immunoblastic with plasmacytoid features. Small noncleaved lymphomas (*e.g.*, Burkitt lymphoma, non-Burkitt types) also occur in these patients.

McGrath and associates studied three cases of HIV-associated, disseminated, large cell (*i.e.*, immunoblastic) lymphoma at necropsy.[103] All three cases had an identical phenotype at different tumor sites as determined by immunohistochemical analysis: IgM-positive B cells. However, by immunoglobulin gene rearrangement, they were able to demonstrate monoclonality only in a few tumor sites in all three patients. Several foci of monoclonal disease were observed in one patient, but other histologically identical metastases were negative for this characteristic. Unlike the immunoblastic lymphomas seen in transplant patients, two of the three patients showed no evidence of EBV sequences; in the remaining patient, a minor clone of EBV-infected cells was found, but only at one site. The researchers concluded that EBV-negative polyclonal large cell lymphomas may be a distinct disease entity unique to HIV-infected persons. In contrast to HIV-associated Burkitt lymphoma, no *MYC* rearrangements were found at any sites in their three patients.

Nasr and colleagues reported the first case of a pulmonary T-cell lymphoma of the large cell immunoblastic type with a helper phenotype in an AIDS patient.[104] Mittal and associates described a case of angiocentric malignant lymphoma with features of lymphomatoid granulomatosis and B-cell phenotype that was identified by cell surface markers and Southern blot test.[105] Unlike most cases of lymphomatoid granulomatosis that represent T-cell lymphomas in patients with AIDS, the disease may represent multiclonal selection of B lymphocytes associated with EBV infection.

Pluda and colleagues reported a cohort of 55 patients followed at the National Cancer Institute for an extended period on a prolonged antiretroviral therapy with zidovudine or zidovudine-containing regimens.[106] Eight patients (14.5%) developed high-grade NHL at extranodal sites and had received therapy for a median of 23.8 months (range, 13–34.5 months) before developing NHL. Using the Kaplan-Meir method, the researchers estimated the probability of developing NHL after 36 months of therapy to be 46.4%, an extraordinarily high figure. All the patients had CD4 T lymphocyte counts below 50 for a median of 15.3 months (range, 5.5–35 months) before developing NHL.

Hodgkin lymphoma (HL) and other hematologic malignancies occur much less frequently in patients with AIDS. Guarner and associates described the simultaneous existence of HL and NHL.[107] HL was identified in retroperitoneal lymph nodes, liver, and spleen. One periaortic lymph node contained NHL of the diffuse large cell type. EBV was identified in both lymphomas using hybridization techniques. Lymphomas are rare in children with AIDS, but Young and Crocker reported a case of disseminated Burkitt lymphoma with pulmonary involvement in a child who had had LIP.[108]

Heitzman called attention to a condition resembling angioimmunoblastic lymphadenopathy in children with AIDS.[109] Monfardini and colleagues reported from Italy a series of 49 HIV-related tumors other than malignant lymphoma and Kaposi sarcoma.[110] There were five patients with acute lymphoblastic leukemia, the immunophenotype of which was Burkitt type (L3), one patient with acute myeloblastic leukemia (M2), one patient with chronic lymphocytic leukemia, two young adults with multiple myeloma, and one patient with thymoma.

Other Neoplasms

In 1984, Irwin and associates reported a 35-year-old man with adenosquamous carcinoma of the lung metastatic to the scapula

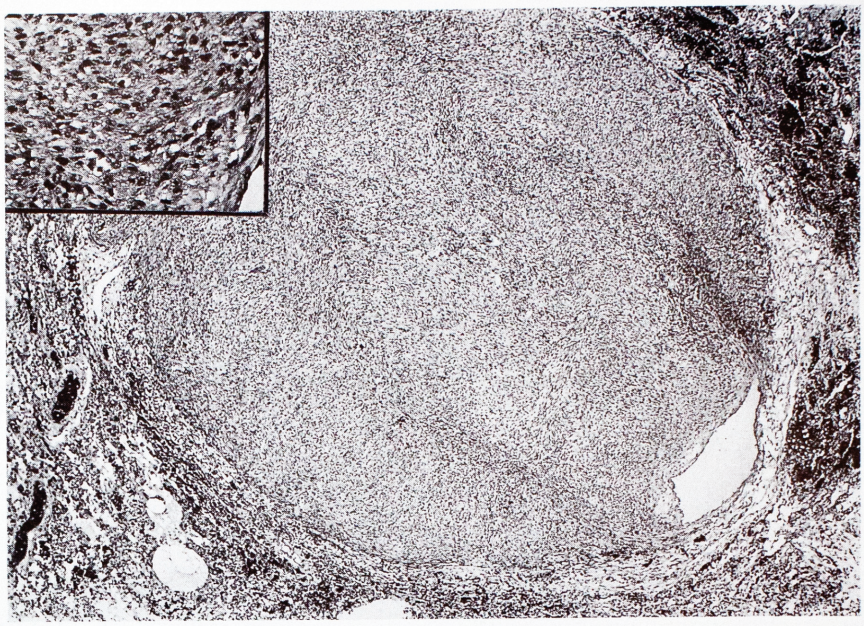

FIGURE 45-19. Peculiar smooth muscle proliferation arose in the wall of a pulmonary vein in a child with human immunodeficiency virus infection. (H & E stain; low magnification.) The spindle cell proliferation is characteristic of the tumor (*inset*). (H & E stain; intermediate magnification; from Saldana MJ, Mones JM. Lymphoid interstitial pneumonia in HIV-infected individuals. Prog Surg Pathol 1992;12:81.

and mediastinal lymph nodes.[111] The following year, Nusbaum detailed the case of a 45-year-old homosexual man with a 30-pack-year smoking history and AIDS who developed cavitary small cell carcinoma of the lung with hepatic metastasis.[112] The research teams led by Monfardini, Braun, and Sridhar reported series of patients with lung cancer and HIV infection.[110,113,114] All of Braun's six patients were younger than most patients with lung cancer (mean, 40 years; range, 30–48 years).[113] The radiographic findings did not differ from those of typical lung cancer and consisted of pulmonary and pleural masses, effusions, and mediastinal adenopathy. Four patients had adenocarcinoma, but one patient had small cell carcinoma, and one had squamous cell carcinoma. The investigators identified those six patients out of 500 HIV-infected persons and extrapolated the findings to represent 1200 cases per 100,000 persons, corresponding to a 14-fold increase in risk of developing lung cancer when compared with the normal risk of 85 per 100,000.

In their series of 19 patients with HIV infection and lung cancer, Sridhar and colleagues found similar results.[114] All patients were men and significantly younger (mean, 48 years) than most lung cancer patients. Most patients smoked cigarettes, and adenocarcinoma was the most common histologic subtype. The median survival was 3 months, with none surviving more than 10 months. In a large study of 49 HIV-related tumors, Monfardini and associates found eight pulmonary carcinomas (*i.e.*, four adenocarcinomas, two small cell carcinomas, one mesothelioma).[110] The most common tumors in their series were germ cell tumors of the testes (12 patients), represented by six seminomas, two embryonal carcinomas, and four embryonal-mixed tumors. Nine cases of cervical carcinoma, three central nervous system tumors (*i.e.*, two glioblastomas, one medulloblastoma), three colorectal and anal carcinomas, nine patients with hematologic malignancies, and single miscellaneous tumors in the oral cavity, pancreas, thyroid, kidney, thymus, and skin (*i.e.*, malignant melanoma) were identified.

Rare smooth muscle tumors (*e.g.*, leiomyomas, leiomyosarcomas) have been identified in children with HIV infection.[115,116] They commonly involve the lung and gastrointestinal tract. We have had the opportunity of studying one such patient who also had LIP (Fig. 45-19).[19]

Pulmonary hypertension

A syndrome identical to primary pulmonary hypertension is presently a well-recognized manifestation of HIV infection. Vascular changes in these patients include muscular medial hypertrophy of pulmonary arteries with concentric intimal fibrosis; necrotizing arteritis and plexiform lesions have also been noted. In 1987, Kim and Factor reported the first example of HIV-related pulmonary hypertension in a homosexual man who also had mesangioproliferative glomerulonephritis.[117] Goldsmith and colleagues noted comparable changes in five hemophiliacs.[118] According to Speich and colleagues, HIV-related pulmonary hypertension may effect up to 8.1% of HIV-positive patients with cardiopulmonary complaints.[119] Mette and colleagues[120] and Coplan and associates[121] believe that the mechanisms of production of the vascular changes are humoral. However, neither of the two patients reported by Mette and colleagues,[120] in whom they failed to demonstrate the virus in the pulmonary lesions, had necrotizing vasculitis or plexiform structures. We have reported the case of a Haitian with AIDS, LIP, necrotizing vasculitis, and plexiform lesions.[19]

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