Pulmonary Complications of HIV Infection

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Objectives:

1. To discuss the types of pulmonary disorders that occur in patients with HIV infection.
2. To understand how demographic factors, the degree of immunosuppression, and the application of antipneumocystis prophylaxis and antiretroviral therapy influence risk of developing different types of pulmonary disorders.
3. To summarize the clinical, radiographic, and laboratory features of infections and neoplasms in patients with HIV infection.
4. To discuss the diagnostic evaluation and treatment of HIV-associated pulmonary disorders.

Key words: bacterial pneumonia; cytomegalovirus; fungi; HIV; Kaposi's sarcoma; mycobacteria; *Pneumocystis carinii*; pulmonary diseases

The AIDS epidemic is one of the most important global health problems of the 20th century. By July 2001, almost 800,000 cases of AIDS were reported in the United States, but the impact of AIDS in Africa and Asia is far more devastating. In developed nations, the rates of opportunistic infections and death in persons with AIDS have declined dramatically since 1995 because of advances in the treatment of human immunodeficiency virus (HIV), and there is new hope that AIDS may not be uniformly fatal. Nevertheless, around 40,000 Americans are infected with HIV each year, and in many urban communities, AIDS-related diseases are still the leading causes of death among young adults. Despite the apparent success of highly active antiretroviral therapy, its long-term efficacy is not yet known, and it is too expensive to be available at all to millions of persons with AIDS worldwide.

Patients with HIV infection usually die of infection, and the lung is a frequent target. Noninfectious pulmonary disorders are also common in HIV-infected persons. Table 1 lists the infectious, neoplastic and inflammatory diseases that occur in patients with HIV infection, and their typical radiographic patterns are summarized in Table 2.

Epidemiology

At the beginning of the AIDS epidemic in 1980, most patients were homosexual and bisexual men. The epidemiology of HIV infection in the United States has moved toward injection drug users and their sexual partners, influencing types of infections that occur when the immune system is compromised. The 103,500 cases reported to CDC in 1993 after the AIDS surveillance definition was

Table 1— *HIV-Associated Respiratory Disorders*

Bacterial pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Pseudomonas aeruginosa
Staphylococcus aureus
Moraxella catarrhalis
Rhodococcus equii
Mycobacterium tuberculosis
Mycobacterium avium complex
Other nontuberculous mycobacteria

Fungal infections
Pneumocystis carinii
Cryptococcus neoformans
Histoplasma capsulatum
Aspergillus fumigatus
Coccidioides immitis
Blastomyces dermatitides

Protozoal infections
Strongyloides stercoralis
Toxoplasma gondii

Viral infections
Cytomegalovirus
Adenovirus
Herpes simplex

Malignancies
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Carcinoma of the lung

Other Disorders
Sinusitis
Bronchitis
Bronchiectasis
Emphysema
Lymphocytic interstitial pneumonitis
Nonspecific interstitial pneumonitis
Bronchiolitis obliterans organizing pneumonia
Primary pulmonary hypertension
Immune reconstitution syndromes

expanded to include bacterial pneumonia, tuberculosis, and severe immunosuppression (as defined by a CD4+ lymphocyte count < 200/μL) and included disproportionate numbers of injection drug users and women. The percentage of persons with AIDS who are injection drug users and women is increasing annually, and racial and ethnic minorities are disproportionally represented, even among gay men. Among US persons reported with AIDS in 2000, 69% were black or Hispanic.

HIV-Associated Pulmonary Disorders

The pulmonary disorders associated with HIV infection range from mild abnormalities in pulmonary function unaccompanied by symptoms to fulminating opportunistic infections. The risk for developing each of these disorders is strongly influenced by the severity of immunosuppression, the patient's demographic characteristics and place of current or prior residence, and whether they are using prophylaxis against common HIV-associated infections. Genetic factors are probably also important but less precisely defined.

Influence of Immune Function

The severity of the abnormality in host defense is a primary determinant of the risk of developing specific pulmonary disorders. Early in the course of HIV infection, when the immune system is not severely compromised, respiratory disorders may occur similar to those in the general population. Opportunistic infections occur only with severe immunodeficiency.

The CD4+ lymphocyte count is still the most reliable surrogate marker for immune function, risk of opportunistic infection, and risk of progression of HIV disease. Measurement of HIV activity with serum HIV RNA ("viral load") is now used routinely to assess response to treatment with antiretrovirals and to stratify patients by risk of progression of disease but is a less reliable predictor than CD4+ count in determining risk of developing specific HIV-related diseases. In a survey of the medical records of more than 18,000 HIV-infected subjects who received care in more than 100 sites in ten U.S. cities, common disorders like sinusitis, bronchitis, and pharyngitis occurred at all strata of CD4+ cell counts (Table 3). With lower counts, different pulmonary infections occurred with increasing frequency. Some opportunistic infections tend to occur only with severe immunodeficiency (CD4+<100/μL), including disseminated nontuberculous mycobacterioses, disseminated fungal infections, central nervous system toxoplasmosis, and cytomegalovirus disease. Therefore, common respiratory problems like sinusitis and bronchitis may occur at any CD4+ count, and

Table 2—*Selected Disease Conditions Listed by Usual CD4+ at Time of Diagnosis*

CD4+>500/μL
Sinusitis/mastoiditis/otitis
Bronchitis
Pharyngitis
Lung Cancer
CD4+ < 400//μL
Bacterial pneumonia
Pulmonary *M tuberculosis*
Cardiomyopathy
CD4+ < 200/μL
P. carinii pneumonia
Kaposi's sarcoma
Bacterial sepsis
Disseminated *M tuberculosis*
CD4+<100/μL
Disseminated *Mycobacterium avium* complex
Cytomegalovirus disease
Disseminated fungal infections

*Adapted from Hanson et al.

Table 3—*HIV Infection: Chest Radiographic Patterns and Common Etiologies*

Focal Infiltrates	Mediastinal Lymphadenopathy
Bacteria	*M tuberculosis*
M tuberculosis	*M avium-intracelluare*
P carinii	Kaposi's sarcoma
	Lymphoma
	Fungi
Diffuse Infiltrates	Pleural Effusion
P carinii	Bacteria
M tuberculosis	*M tuberculosis*
Kaposi's sarcoma	Kaposi's sarcoma
Bacteria	Lymphoma
Fungi	Fungi
Cytomegalovirus	Cardiomyopathy
	Hypoproteinemia
Diffuse Nodular Infiltrates	Cavitation
Kaposi's Sarcoma (large nodules)	*M tuberculosis* (high CD4+)
M tuberculosis (miliary)	*P carinii* (low CD4+)
Fungi (small nodules)	*P aeruginosa* (low CD4+)
	R equi
	Fungi
Pneumothorax	
P carinii	

bacterial pneumonia and tuberculosis often occur before AIDS-defining opportunistic infections and neoplasms. Declining immune function increases the risk for all HIV-associated respiratory disease.

Demographic Factors

The increasing proportion of injection drug users in the HIV-infected population was accompanied by the recognition of bacterial pneumonia and tuberculosis as important HIV-associated infections. Several cohort studies show that bacterial pneumonia is more common than *Pneumocystis carinii* pneumonia (PCP), and the risk of developing bacterial pneumonia is significantly higher in injection drug users than in others.

Race and ethnicity may also influence the risk of developing bacterial pneumonia and tuberculosis, but these associations are confounded by differences in access to health care, the higher prevalence of tuberculosis in minority communities, and disproportionally high numbers of injection drug users who are black or Hispanic. Nevertheless, the risk of tuberculosis is higher in blacks and Hispanics than whites, while whites have a higher risk of PCP, HIV-associated malignancies, and cytomegalovirus disease.

Residence

The place of residence strongly influences the risk of developing specific infections. The high incidence of PCP in the United States and Europe contrasts sharply with Africa, where it is much less common. It is still unknown whether genetic or environmental factors account for the lower incidence of PCP in Africa. In the US, the incidence of HIV-associated tuberculosis is highest in the Northeast. The geographic distribution of endemic fungi is a strong determinant of risk of those infections; disseminated histoplasmosis and coccidioidomycosis are common in patients with AIDS who live in endemic areas. These infections may also occur as reactivation disease after HIV-infected persons move to other areas and develop immunocompromise.

Use of Prophylaxis and HAART

The risk of developing specific opportunistic infections declines with the use of prophylaxis. Even before the availability of highly active antiretroviral therapy (HAART), the incidence and mortality due to PCP and tuberculosis was declining, attributable to the use of prophylaxis by susceptible persons. Following the widespread use of HAART around 1996, the incidence of opportunistic infections and death among HIV-infected persons has declined dramatically because successful antiretroviral therapy inhibits viral replication and restores immune function. However, immune reconstitution is associated with the development of other clinical syndromes, discussed later.

Bacterial Pneumonia

The importance of bacteria as HIV-associated pulmonary pathogens was established by investigations in patients who did not have advanced immunosuppression. HIV infection impairs humoral immunity through quantitative and functional defects in CD4+ lymphocytes. This increases the risk of developing bacterial infections, including sinusitis and pneumonia. Although a first episode of bacterial pneumonia usually occurs before the diagnosis of AIDS, the risk of developing pneumonia increases as the CD4+ lymphocyte count declines. Injection drug users are at higher risk than other groups, and neutropenia is an independent risk factor. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) appears to reduce the risk of developing bacterial pneumonia. Bacterial pneumonia may also accelerate the course of HIV disease, since it is an independent predictor of progression to AIDS and mortality.

Encapsulated organisms, especially *Streptococcus pneumoniae* and *Haemophilus influenzae,* are the most frequent pathogens (Table 1). Although pneumonia due to atypical pathogens like Mycoplasma and Legionella is described, it is relatively uncommon. *Rhodococcus equii,* an aerobic Gram-positive acid-fast bacillus, may cause focal consolidation, endobronchial disease, and cavitation, usually in patients with advanced HIV disease. Patients with very low CD4+ lymphocyte counts (typically $< 50/\mu L$) may develop pneumonia due to *Pseudomonas aeruginosa*, even in the absence of risk factors such as neutropenia, corticosteroid use, and hospital-acquired infection. *Nocardia asteroides* may cause nodules, consolidation, cavitation, pleural effusions, empyema, and intrathoracic lymphadenopathy in patients with HIV infection.

The diagnosis and treatment of bacterial pneumonia in persons with HIV infection is, in almost all respects, the same as for HIV-uninfected patients. Patients usually present with fever, chills, productive cough and localized areas of consolidation on chest radiograph. While this clinical picture strongly suggests bacterial pneumonia, it may also occur with tuberculosis and fungal infection. Conversely, patients with bacterial pneumonia may have diffuse pulmonary opacities that resemble PCP.

Polyvalent pneumococcal vaccine is recommended for all HIV-infected people, although individuals with low CD4+ counts are less likely to mount an adequate antibody response. A vaccine against *H influenzae* type b is available, but its use in patients with HIV infection is of limited use, since most infections are with strains that cannot be typed. Although influenza vaccine is also recommended, there are no data indicating that patients with HIV infection are at increased risk of contracting influenza, or that the illness is more severe than in the general population.

Pneumocystis carinii Pneumonia

Diagnosis

The incidence of PCP is declining in the United States, attributed to the use of HAART and antipneumocystis prophylaxis. Nevertheless, PCP is still an important cause of opportunistic infection. Patients who develop PCP are either not receiving medical care, do not adhere to medical regimens, or are prescribed treatments that are either intolerable or ineffective. The organism is classified as a fungus. It is not known whether it is acquired from an environmental source, by person-to-person transmission, or both. PCP usually progresses insidiously, with gradually increasing dyspnea over weeks; it sometimes presents as an acute illness with rapid deterioration over a few days. The chest radiograph usually has diffuse granular opacities, which strongly suggests the diagnosis. Some patients with PCP have nodular densities, lobar consolidation, or normal films. Cystic abnormalities and spontaneous pneumothoraces in patients with known or suspected HIV infection are usually caused by PCP.

Adjunctive testing may support the diagnosis of PCP. This infection is unlikely in a patient who had a CD4+ cell count above 200 / μL in the preceding 2 months in the absence of other HIV-associated symptoms. Approximately 90% of patients with PCP have an elevated serum lactic dehydrogenase (LDH), but this may occur with other pulmonary diseases. Oxygen desaturation with exercise is a relatively sensitive and specific test in patients suspected to have PCP but is not diagnostic. Gallium 67 and indium 111 lung scans are highly sensitive indicators of PCP, but isotope uptake also occurs in other pulmonary infections, so they are seldom useful in the diagnosis.

Microbiologic Diagnosis

P carinii cannot yet be cultured *in vitro*, so the diagnosis of PCP can be confirmed only by demonstrating organisms in a lung-derived specimen. The least invasive diagnostic test is the analysis of sputum induced with 3% saline solution delivered by ultrasonic nebulization. Using modified Giemsa, methenamine silver, or immunofluorescent staining, and depending on the experience of the laboratory, *P carinii* can be identified in up to 80% of cases. Other pathogens, particularly *Mycobacterium tuberculosis* and fungi, may also be found using appropriate staining and culture techniques.

It is controversial whether to routinely proceed with fiberoptic bronchoscopy to confirm the diagnosis of PCP in patients who have nondiagnostic sputum specimens. Some prefer to treat these patients empirically for PCP and establish a diagnosis only if there is no clinical response within 5 days. Proponents of empiric therapy hold that a presumptive diagnosis of PCP is usually accurate, and that the procedure usually carries unnecessary inconvenience, risk, discomfort to patients, and expense. Proponents of early bronchoscopy maintain that routinely using an empiric approach will subject many patients to treatment and its attendant toxicity for a disease that they do not have, and nonresponders may be to ill to undergo bronchoscopy after several days of inappropriate therapy. Coinfection with other pathogens is common and may not be diagnosed in patients treated empirically. Also, adjunctive corticosteroid therapy may transiently improve symptoms in patients with other pulmonary disorders, and contribute to the emergence of other opportunistic infections, such as aspergillosis and cytomegalovirus.

If bronchoscopy is done in patients with nondiagnostic sputum specimens, BAL is performed

routinely. The complication rate is very low, and the yield in the diagnosis of PCP is over 90% in most centers. This yield is optimized by performing lavage in more than one lobe and is higher in the upper lobes than the lower. All lavage specimens should be examined for the presence of acid-fast bacilli, fungi, and viral cellular inclusions, since patients with suspected PCP may have another infection or may be co-infected with other pathogens. The role of BAL in the diagnosis of bacterial pneumonia in HIV-infected persons is not established.

Citing the high diagnostic yield of BAL in the diagnosis of PCP, some authors recommend that transbronchial biopsy should be omitted initially and performed during a second bronchoscopy if the lavage is nondiagnostic. However, biopsy is occasionally diagnostic of PCP and other pathogens when the lavage is negative, and it is the least invasive means of diagnosing other pulmonary conditions that require histologic interpretation. Transbronchial biopsy is contraindicated in the presence of bleeding disorders, and the high risk of pneumothorax usually precludes biopsy in patients undergoing mechanical ventilation. Diagnosing PCP with video-assisted thoracoscopy or an open procedure is rarely necessary, since almost all cases are confirmed using sputum induction or bronchoscopy.

Treatment

Trimethoprim-sulfamethoxazole (TMP-SMZ) is the agent of choice, regardless of the severity of disease. It is consistently the most effective in comparative studies and also inexpensive and available in both oral and IV preparations. However, many patients are unable to tolerate the drug for a full course. The optimal duration of treatment is unknown, but most clinicians treat for 14 to 21 days, followed by prophylaxis.

The choice of antipneumocystis treatment depends on the severity of disease and how the patient tolerates the medication (Table 4). Outpatient treatment with oral agents is an option for patients with mild-to-moderate episodes who have a Pa_{O_2} breathing room air >70 mm Hg. For patients with moderate or severe infection, adjunctive therapy with corticosteroids at the start of antipneumocystis treatment reduces the likelihood of developing respiratory failure, deterioration of oxygenation, and death. The precise mechanisms of the beneficial effects of corticosteroids in patients with PCP are

Table 4—*Treatment of PCP*

Drug	Dose	Comments
Moderate-to-severe disease (Pa_{O_2} ≤ 70 mm Hg, or $P_{AO_2} - Pa_{O_2}$ ≥ 35-45 mm Hg breathing room air)		
TMP/SMZ	15-20 mg/kg / 75-100 mg/kg IV or po in 3 divided doses	Drug of choice, but toxicity (rash, fever, nausea) is frequent
Pentamidine isoethionate	3-4 mg/kg IV daily	Toxicity: dysglycemia, renal failure, neutropenia, QT prolongation, arrhythmias, pancreatitis, orthostatic hypotension
Trimetrexate-folinic acid	45 mg/m^2 IV daily- 20 mg/m^2 IV or po q6h	Not as effective as TMP-SMZ, but better tolerated
Prednisone	40 mg po bid, days 1-5 20 mg po bid, days 6-10 20 mg po daily, days 11-21	Recommended as adjunctive therapy, along with an anti-Pneumocystis agent for all patients with PCP who meet criteria for moderate-to severe disease
Mild-to-moderate disease (Pa_{O_2} ≥ 70 mm Hg, or $P_{AO_2} - Pa_{O_2}$ ≤ 35 mm Hg breathing room air)		
TMP/SMZ	Same as above	Most likely to cause hepatotoxicity of all oral regimens
Dapsone-trimethoprim	100 mg po daily - 5-6 mg/kg po tid	Methemoglobinemia and hemolysis in patients with G6PD deficiency
Clindamycin/ primaquine	600 mg IV or po tid/ 15 mg base po daily	Rash, leukopenia, nausea, diarrhea-methemoglobinemia and hemolysis in patients with G6PD deficiency
Atovaquone suspension	750 mg bid	Less effective than TMP-SMZ, but better tolerated

unknown. Patients treated for PCP without corticosteroids often develop deteriorating gas exchange and persistent fever for up to approximately 5 days, presumably related to an inflammatory response to components of killed organisms. Corticosteroids modify these effects, attenuating the initial worsening of oxygenation, and allowing the patient to receive more antimicrobial treatment. Benefit from adjunctive corticosteroids is established in patients who have an arterial oxygen tension <70 mm Hg, or an arterial-alveolar oxygen gradient >35 mm Hg. Patients with less severe abnormalities in gas exchange usually do not benefit, mainly because their outcomes are very good with antipneumocystis treatment alone. Benefit is also questionable when corticosteroids are administered more than 72 h after antipneumocystis treatment has begun.

Adverse reactions to adjunctive corticosteroids occur infrequently. Although life-threatening superinfections are described, they are uncommon. Patients who develop pulmonary disorders shortly after apparently successful treatment of PCP should be evaluated for another opportunistic infection, especially cytomegalovirus.

Prevention

Lifelong antipneumocystis therapy is recommended for all HIV-infected patients with CD4+ cell counts below 200/μL or for patients with HIV-related symptoms, including unexplained persistent fever (>100^{0}F) for 2 weeks, oropharyngeal candidiasis unrelated to antibiotic or corticosteroid therapy, and unexplained weight loss. Prophylaxis can be stopped safely in patients who achieve a sustained increase in CD4+ lymphocyte count to >200/μL after starting HAART. Prophylaxis with TMP-SMZ is most effective but associated with more adverse events requiring discontinuation than aerosolized pentamidine and dapsone. TMP-SMZ is also inexpensive and prevents other infections, including cerebral toxoplasmosis and some strains of pathogenic bacteria. Current expert opinion recommends one double strength tablet (160 mg TMP / 800 mg SMZ) daily, or a single-strength tablet daily if the former is not tolerated. Failure of TMP-SMZ prophylaxis is associated with nonadherence with treatment and with severe immunosuppression as measured by very low CD4+ lymphocyte counts.

Pentamidine administered by aerosol has the potential advantages of high drug levels in the lung with minimal systemic absorption and toxicity. When PCP occurs in patients using aerosolized pentamidine, it is associated with atypical clinical and diagnostic features. Normal regional differences in ventilation make upper lobe distribution of the drug less concentrated than in the lower lung zones, accounting for a higher rate of predominantly upper lobe involvement. These patients are also more likely to have cystic lung lesions and pneumothoraces, and many cases of extrapulmonary *P carinii* are reported, presumably because the drug is delivered only to the lung.

Respiratory Failure Caused by PCP

Despite the use of HAART, antipneumocystis prophylaxis and declining mortality rates from PCP, several studies demonstrate that PCP is still a common cause of respiratory failure and admission to ICUs in patients with AIDS. When treatment of PCP is postponed or ineffective, a clinical syndrome develops that resembles the acute respiratory distress syndrome (ARDS), with severe hypoxemia, intrapulmonary shunt, reduced pulmonary compliance, and the radiographic appearance of diffuse opacities. Just as severe PCP clinically resembles ARDS, the supportive treatment, including intubation, mechanical ventilation, and application of positive end-expiratory pressure, is similar. Continuous positive airway pressure (CPAP) delivered by face mask may improve gas exchange without endotracheal intubation, but its usefulness is limited in patients with severe disease. However, it may afford the patient and physician more time to consider whether mechanical ventilation is desirable. Patients who require mechanical ventilation for PCP have a high mortality rate, possibly related to failure of prophylaxis, antipneumocystis treatment, or adjunctive corticosteroid therapy. When respiratory failure follows several days of appropriate therapy for PCP, the probability of survival is only around 20%. However, the prospects for long-term survival if the patient recovers are far more hopeful than earlier in the epidemic.

Tuberculosis

Coinfection with HIV and *M tuberculosis* is discussed in detail in the chapter by Dr. Ashkin. Modest reductions in cell-mediated immunity increase the risk of reactivation of latent tuberculosis,

and the risk increases as CD4+ cell counts decline. In HIV-infected persons, tuberculosis often occurs before the development of opportunistic infections, probably because *M tuberculosis* is more virulent. In patients with mild immunodeficiency, the clinical presentation is similar to tuberculosis in HIV-negative patients. Atypical pulmonary presentations, including diffuse infiltrates, miliary patterns, intrathoracic lymphadenopathy or normal chest radiographs occur more frequently in patients with advanced immunosuppression (Table 2). These patients also have a high incidence of extrapulmonary infection, including pleura, lymph nodes, gastrointestinal tract, bone marrow, and blood.

The diagnosis of tuberculosis may be difficult in HIV-infected persons. Cutaneous anergy is more prevalent as CD4+ cell counts decline, making tuberculin skin tests less useful. Radiographic clues to the diagnosis include cavitation, hilar and mediastinal lymphadenopathy, and pleural effusions. When there is cavitation, acid-fast smears and cultures of sputum are usually positive. In patients who do not expectorate spontaneously, sputum may be induced with hypertonic saline solution. Bronchoscopy with BAL, transbronchial biopsy, and postbronchoscopy sputum is often diagnostic. Biopsy specimens enhance the immediate diagnostic yield of bronchoscopy in the diagnosis of pulmonary TB compared with BAL alone.

Despite an appropriate evaluation, acid-fast smears of sputum and bronchoscopic specimens may be negative, and cultures may not be positive for several weeks. Early treatment of tuberculosis improves the outcome and reduces transmission of the disease to others, so initial empiric therapy is warranted for patients with radiographic abnormalities consistent with TB, unless another disorder is identified.

Atypical Mycobacteria

Mycobacterium avium complex (MAC) causes devastating complications and death in patients with severe immunosuppression. Patients may have persistent fever, wasting, and diarrhea. However, MAC is rarely a pulmonary pathogen in patients with AIDS. Its isolation in patients with symptomatic pulmonary disease usually occurs in association with another pathogen, such as *P carinii*. Other nontuberculous mycobacteria also cause pulmonary infection in patients with HIV infection. However, if acid-fast bacilli are identified from sputum or bronchoscopic specimens, patients should be treated presumptively for *M tuberculosis* until culture results are known, mainly because tuberculosis is more common, has a better response to treatment, and because early treatment of active tuberculosis is an essential public health measure.

Cytomegalovirus

In patients with CD4+ lymphocyte counts <50/μL, cytomegalovirus (CMV) commonly causes retinitis, esophagitis, gastritis, colitis, hepatitis, encephalitis, and death. Patients with AIDS can also have CMV pneumonitis, but this is uncommon. Although the virus is often isolated in cultures of BAL fluid, it is not usually pathogenic. Pulmonary infection can be inferred when typical intranuclear or intracytoplasmic inclusions are found in BAL fluid or biopsy material. The likelihood that CMV is a pulmonary pathogen is also greater when CMV infection is found at other sites.

CMV pneumonitis usually occurs in patients who have had prior AIDS-defining illnesses. They present with a clinical syndrome similar to PCP, with dyspnea, nonproductive cough, fever, and diffuse pulmonary opacities. Unilobar radiographic involvement, cavitation, nodules, and pleural effusions are also described. It is treated the same as infection in other sites, with IV gancyclovir or foscarnet, and the response to therapy are is similar to that of CMV retinitis or gastrointestinal disease. Since CMV infection occurs only in patients with very severe immunosuppression, the long-term prognosis is very poor.

Fungal Pneumonias

Fungal infections are discussed in detail in the chapter by Dr. Sarosi. Life-threatening fungal disease may occur in HIV-infected patients, either by new infection or reactivation of latent disease. The types of fungal infections depend upon the severity of immunodeficiency and whether the patient has lived in endemic areas.

Cryptococcosis

Cryptococcosis neoformans is distributed throughout the world and is the most common

fungus causing life-threatening illness in patients with AIDS. The meninges are the most common site of infection, and cryptococcal meningitis is often the first manifestation of AIDS. With cryptococcal pneumonia, the chest film usually shows diffuse infiltrates, similar to PCP, but localized infiltrates, nodules, cavitation, pleural effusions, miliary patterns, and lymphadenopathy are also seen. Most patients with cryptococcal pneumonia have meningitis and disseminated disease, and CD4+ lymphocyte counts are typically below 100/μL. The diagnosis is established by identification of the organism from sputum, BAL fluid, pleural fluid, or lung biopsy. A high titer of cryptococcal antigen in serum is strongly suggestive, and an antigen titer >1:8 in BAL fluid is diagnostic of cryptococcal pneumonia.

Histoplasmosis

Histoplasmosis capsulatum is endemic in the Ohio and Mississippi river valleys, Central and South America, and the Caribbean islands. Patients with HIV infection who come from endemic areas may develop disseminated disease when immunodeficiency permits reactivation of latent infection. The clinical presentation is usually subacute and the chest roentgenogram typically shows a diffuse or miliary pattern, although localized infiltrates may occur. The diagnosis is established by identification or culture of the organism from blood, lung-derived specimens, bone marrow, or liver.

Amphotericin B is the treatment of choice for most cases of HIV-associated histoplasmosis. Itraconazole, 200 mg twice daily, is an alternative in patients with milder disease and should be used as chronic suppressive therapy for life after the primary infection is controlled.

Aspergillosis

Patients with advanced immunosuppression may develop life-threatening pulmonary aspergillosis. Two common patterns of disease are identified: an invasive parenchymal infection, which is usually fatal, and a predominantly bronchial disease presenting with dyspnea and airway obstruction. The classical risks for Aspergillus infection, namely prolonged neutropenia and treatment with high-dose corticosteroids, are often absent. Patients with advanced AIDS probably develop aspergillosis because of defects in neutrophil or alveolar macrophage function. The CD4+ lymphocyte count is typically <30/μL, and the prior use of corticosteroids and neutrophil counts <500/μL increase the risk. Disseminated disease is common, especially to the brain.

Clues to the diagnosis of invasive pulmonary aspergillosis include upper lobe disease with cavitation and hemoptysis. This diagnosis has traditionally required histologic proof, since Aspergillus is ubiquitous, and its presence in nasopharyngeal secretions, sputum, and BAL may represent contamination or colonization. However, recent studies in patients with severe immunosuppression, including AIDS, indicate that the isolation of Aspergillus in BAL fluid correlates strongly with histologic proof of tissue invasion.

Other Fungal Infections

In endemic areas, disseminated coccidioidomycosis and blastomycosis may occur in patients with AIDS, usually as a complication of advanced immunosuppression. Some patients may develop reactivation of prior infection after moving from an endemic area. These infections usually involve the lung, presenting with cough, fever, dyspnea, and the appearance of nodular, focal, cavitary, or diffuse disease. The diagnosis is established by demonstrating the organism by microscopy or culture in respiratory specimens.

Neoplastic Diseases of the Lungs

Kaposi's Sarcoma (KS)

This is the commonest malignancy in persons with HIV infection, and the skin is the major site of involvement. KS is caused by human herpevirus 8 (HHV-8). This virus infects many healthy adults and can be isolated commonly in saliva, prostate tissue and semen. It is probably transmitted by sexual contact and causes disease when activated by HIV-associated immunosuppression. This hypothesis helps to explain why KS is much more common among HIV-infected gay men than in other transmission groups.

KS may involve many organs, including the lung. Patients with pulmonary KS usually have obvious mucocutaneous lesions, but the lung may be the only site of disease in up to 15% of cases.

Involvement of the airways, parenchyma, pleura, and intrathoracic lymph nodes causes a diverse range of symptoms and radiographic findings. The majority of patients with pulmonary KS diagnosed antemortem have cough, dyspnea, and fever.

In the airways, KS lesions are usually asymptomatic but sometimes cause obstruction or hemoptysis. The finding of typical lesions on inspection of the airways is usually considered diagnostic. Histologic diagnosis may be difficult because the yield of forceps biopsy is low. Some authors believe that forceps biopsy of KS lesions places the patient at significant risk of bleeding, but this is controversial.

Parenchymal involvement with KS is suggested by bronchial wall thickening, nodules, Kerley B lines, and coexisting pleural effusions, especially in patients with cutaneous disease. Bronchoscopy can determine whether diffuse radiographic opacities are caused by KS or an opportunistic infection. The yield of bronchoscopic lung biopsies in the diagnosis of KS is low, and even open lung biopsy is nondiagnostic in approximately 10% of cases because of the focal distribution of lesions. Therefore, the diagnosis of pulmonary parenchymal KS is usually inferred in patients with cutaneous disease, chest radiographs that suggest this disorder, visual confirmation of airway lesions, and no evidence of opportunistic infection on BAL or bronchoscopic lung biopsy. Patients with parenchymal opacities who have typical lesions in the airways and no identified pulmonary infection are assumed to have parenchymal KS.

When KS involves the pleura, effusions are usually exudative and sanguinous, but the cytologic examination is nondiagnostic. Closed pleural biopsy specimens are rarely positive due to the focality of pleural lesions and predominant involvement of the visceral, rather than parietal pleura. Since establishing a diagnosis usually necessitates a thoracoscopic or open pleural biopsy, the presence of pleural involvement with KS is usually inferred in a patient with cutaneous disease and a serosanguinous effusion without a reasonable alternative explanation.

Lymphoma

Non-Hodgkin's B-cell lymphoma is associated with HIV infection, and unlike most other HIV-related disorders, it continues to occur despite the use of HAART. Although pulmonary involvement is usually clinically innocuous, the lung is a common site of extranodal disease. If symptoms occur, they are usually late in the course of HIV disease and simulate common opportunistic infections. Even in patients with an established diagnosis of lymphoma, lung involvement is usually a late feature of HIV disease. It may present with lobar consolidation, nodules, reticular opacities, and masses. The biopsy is established by bronchoscopic or open biopsy; BAL has a very low diagnostic yield.

Involvement of the intrathoracic lymph nodes is manifested radiographically by lymphadenopathy, pleural involvement by effusions and pleural thickening, and the airway involvement by atelectasis. The diagnosis is established by biopsy or cytologic analyses of pleural fluid.

Carcinoma of the Lung

There is emerging evidence that the incidence of lung cancer is increased in HIV-infected persons. These cancers seem to be more aggressive, diagnosed at a more advanced stage, and associated with shorter survival than lung cancer in HIV-negative persons. Genomic differences were found in a comparison of lung cancers in patients with and without HIV infection. Even if persons with HIV infection are proven to have an increased incidence of lung cancer, this disease is still very rare compared with opportunistic infections and Kaposi's sarcoma.

Other Pulmonary Disorders

Airway Disease

Patients with advanced HIV infection have a predilection for developing chronic bronchitis and bronchiectasis, even if they do not smoke. The CD4+ count is usually low (<100/μL). Standard antimicrobial agents are usually effective, but symptoms are likely to recur, especially when *P aeruginosa* is isolated from the sputum. The role and efficacy of bronchodilators and anti-inflammatory agents in HIV-associated airway disease have not been studied. HIV infection also appears to accelerate the onset of smoking-related emphysema, possibly through cytotoxic lymphocyte activity.

Idiopathic Inflammatory Disorders

Pulmonary disorders without a defined infectious or neoplastic etiology occur in HIV-infected persons. Lymphocytic interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NIP) are believed to comprise a spectrum of inflammatory changes in response to HIV infection of the lung itself. LIP is most common in HIV-infected children and African-Americans. It may occur as part of a systemic CD8 lymphoproliferative syndrome, with lymphadenopathy, blood lymphocytosis, and involvement of other organs. NIP is very common in persons with low CD4+ counts but is rarely diagnosed because it usually causes no symptoms. When symptomatic, both LIP and NIP are treated with corticosteroids. Bronchiolitis obliterans organizing pneumonia (BOOP) has a similar clinical presentation in patients with and without HIV infection. Lung biopsy, either transbronchial or open, is necessary for the diagnosis. This disorder often improves dramatically with corticosteroids.

Pulmonary Hypertension

Primary pulmonary hypertension also occurs more commonly in HIV-infected patients than in the general population. It may eventually lead to cor pulmonale and death. The mechanisms of HIV infection leading to the development of this disorder is unknown; unlike most HIV-associated disorders, there seems to be no relationship to the degree of immune compromise as assessed by the CD4+ count. The approach to diagnosis and treatment is the same as for PPH in HIV-uninfected persons.

Immune Restoration Syndromes

The effectiveness of HAART in restoring immune function has given rise to a host of new immune restoration syndromes. When treatment of HAART is successful, the number of blood CD4+ lymphocytes increases, as does their activity. Increased immune function then leads to inflammation that may have been otherwise clinically silent, leading to overt clinical illness. "Paradoxical worsening of TB" was described in patients who develop transient worsening of TB-related symptoms following antiretroviral therapy. These patients develop fever with worsening or emergence of cervical intrathoracic lymphadenopathy, pulmonary infiltrates, pleural effusions, or other tuberculous lesions shortly after starting HAART. This phenomenon is associated with restoration of cutaneous reactivity to skin tests. The approach to these patients should be to look for a new infection, and in its absence, to treat symptomatically. Other recent reports describe the development of sarcoidosis and worsening of PCP following initiation of HAART.

Annotated Bibliography

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Hanson DL, Chu SY, Farizo KM, et al. Distribution of CD4+ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses. Arch Intern Med 1995; 155:1537-1542

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In the same study, mortality during the follow-up period was almost fourfold greater in subjects who had an episode of bacterial pneumonia than in others. Prophylaxis with TMP-SMZ was associated with a significant reduction in the incidence of bacterial pneumonia.

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Trimethoprim-sulfamethoxazole is more effective than aerosolized pentamidine and dapsone in preventing both PCP and toxoplasmosis, but discontinuing this agent due to adverse reactions is also much more likely. Reducing the dose to one double-strength tablet thrice weekly reduces the risk of toxicity by 43%, without a reduction in efficacy.

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Murray JF, Felton CP, Garay SM, et al. Pulmonary complications of the acquired immunodeficiency syndrome: Report of National Heart, Lung and Blood Institute Workshop. N Engl J Med 1984; 310:1682-1688

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These articles describe different types of immune reconstitution disorders that affect the lung.

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Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 38:853-860

Mortality in a cohort of 1255 patients with advanced HIV infection declined from 29.4/100 person-years in 1995 to 8.8/100 person-years in 1997, with a corresponding dramatic decline in opportunistic infections, even though the rate use of prophylaxis against PCP and MAC disease remained similar. This study demonstrated that combination antiretroviral therapy in an outpatient cohort dramatically reduced morbidity and mortality related to HIV infection.

Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at <http://www.hivatis.org/guidelines/>. Accessed July 2, 2002

For clinically useful information on antiretroviral therapy, print media are OBSOLETE. This website offers continually updated information and recommendations by reliable and mainstream experts. The information here will NOT be on the Boards, but it defines the state of the art in treatment of HIV infection, with detailed descriptions of specific diagnostic and therapeutic modalities. Pulmonologists who see these patients will be interested in the tables describing drug interactions.

Rodriguez-Barradas MC, Stool E, Musher D. Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS. Clin Infect Dis 1996; 23:76-81

The diagnosis of CMV pneumonia is difficult to establish with certainty, since it is commonly found in association with other pathogens, and may be isolated from lung-derived specimens without histologic evidence of disease. This study describes the clinical and laboratory features of patients with confirmed CMV pneumonia.

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In 476 subjects, failure of prophylaxis correlated with the degree of reduction in the CD4+ lymphocyte count. More than 85% of the 92 failures of prophylaxis occurred in persons with counts less than 75/μL.

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These are current. Comprehensive, and continually updating guidelines for the prevention of opportunistic infections in persons with HIV infection. They emphasize prevention of PCP, tuberculosis, toxoplasmosis and MAC.

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In a large multicenter prospective study of HIV-infected subjects who did not have AIDS (1987 definition) at the time of enrollment, the most frequent respiratory diagnoses were also common in the general population: upper respiratory infections, acute bronchitis and sinusitis. Bacterial pneumonia and PCP occurred significantly more frequently in subjects whose CD4+ count at enrollment was < 250/μL, and bacterial pneumonia was more common in injection drug users compared with others.

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Lung cancers in patient with HIV infection have a greatly increased incidence of microsatellite alterations than in others with lung cancer. These differences reflect genomic instability and provide evidence for a link between HIV infection and lung cancer.

Notes

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