MEDICAL GRAND ROUNDS

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PULMONARY DISEASE IN AIDS PATIENTS: AN UPDATE

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New things are made familiar,
and familiar things are made new.

-- Samuel Johnson
Lives of the Poets

INTRODUCTION

In 1981 the Centers for Disease Control (CDC) began to receive reports of an outbreak of pneumocystis carinii pneumonia (PCP) in previously healthy homosexual men (1,2). Indeed in one month the request to the CDC for Pentamidine (then a restricted drug) exceeded the total number of requests in the previous decade. These occurrences, along with reports of Kaposis sarcoma, generalized lymphadenopathy and unusual bowel pathogens in gay men alerted the medical community to the presence of a new acquired immunodeficiency syndrome (AIDS). Since 1981 the characteristics of this disorder have become widely known to both medical and lay personnel.

Pulmonary disease continues to account for a major portion of both morbidity and mortality in AIDS patients (3). Experience with pulmonary disease in patients infected with the human immunodeficiency virus (HIV) is now widespread and most internists are familiar with the presentation and management of these disorders. However, several important changes in the pattern of pulmonary disease have recently become apparent. Because these changes have implications for the diagnosis, management and outcome of AIDS patients it is worthwhile to update our knowledge of pulmonary disease in HIV-infected individuals as we approach the end of the first AIDS decade.

DEFINITION

Prior to 1987 the presence of an indicator disease (such as PCP, Kaposis sarcoma etc...) was required to establish a diagnosis of AIDS. However, the widespread availability of testing for antibody to HIV has altered the necessity of securing specific tissue or microbiologic diagnoses prior to making a diagnosis of AIDS. Any HIV-positive individual with

1) A history of dyspnea on exertion or nonproductive cough of less than 3 months duration;

2) Radiographic evidence of bilateral infiltrates;

3) An arterial PO_2 < 70 mmHg on room air or an abnormal lung diffusion capacity (D_LCO) and

4) No evidence of bacterial pneumonia

is now considered to fulfill the criteria for a presumptive diagnosis of AIDS (4). Indeed the emphasis on a clinical diagnosis has resulted in a dramatic decrease in the percentage of AIDS patients undergoing invasive diagnostic procedures. At Parkland Hospital the number of bronchoscopies performed in AIDS patients dropped from 149 in 1987 to 50 in 1989 despite a rise in the number of AIDS patients in Dallas County overall.

Although the diagnosis of AIDS on clinical criteria alone has become more common, the overall spectrum of pulmonary disease secondary to HIV infection remains distinct from other immunodeficiency states (Table 1). The nature of the interaction of HIV with the immune system has thus been the subject of intensive study. Attempts to partially reconstitute the immune defect in AIDS patients are approaching clinical trials and may be particularly germane to the lung where local rather than systemic therapy can theoretically be achieved by an inhalational route. It is therfore important to review the possible effects of HIV infection on pulmonary immune function.

TABLE 1
Pulmonary Disease in AIDS Patients

Pneumocystis Carinii	**>50%**
Nonspecific Interstitial Pneumonitis	
M. Avium Intracellulare	**10-20%**
Kaposis Sarcoma	
M. Tuberculosis	
Fungus	**5-10%**
Bacteria	

PULMONARY IMMUNE FUNCTION IN AIDS

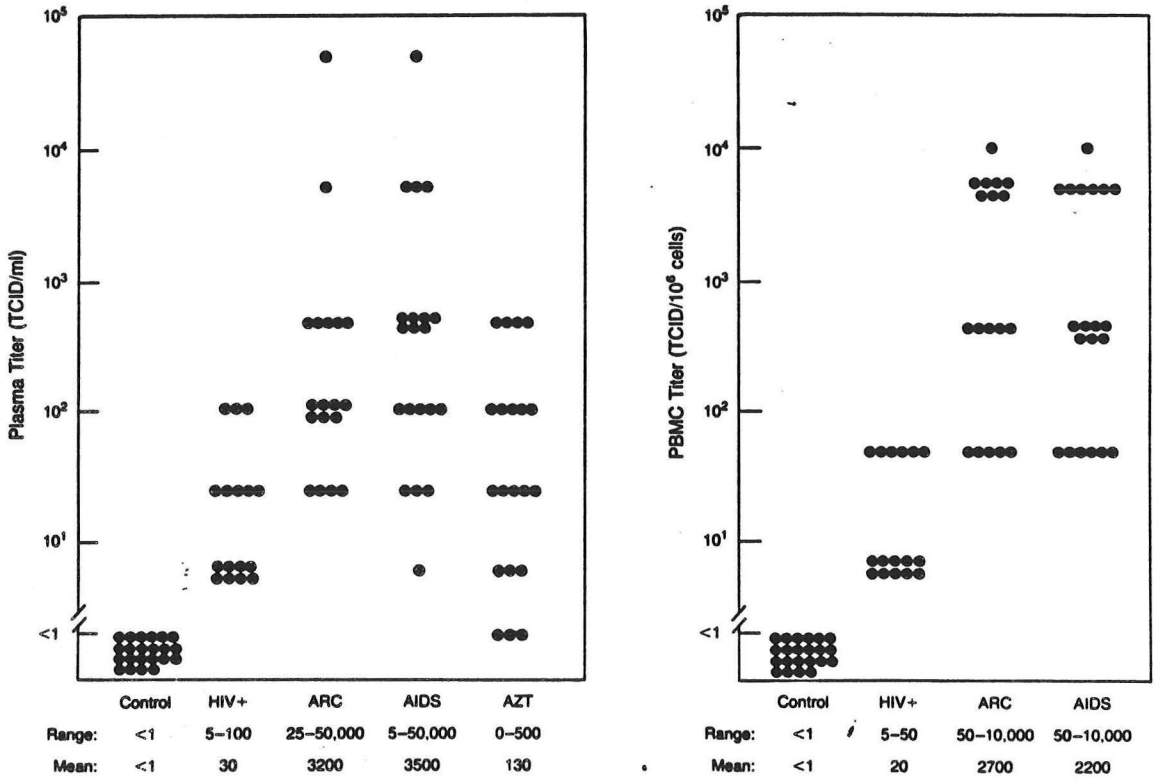
HIV primarily infects cells expressing CD4, the protein which identifies the T helper subset of lymphocytes (5,6). In addition to lymphocytes CD4 is found on other immune cells, most notably macrophages (7,9). In contrast to lymphocytes, macrophages are relatively resistant to the cytopathic effects of the virus and could serve as a reservoir for HIV (10). However, in peripheral blood the reservoir for HIV has clearly been identified as a CD4+ T cell (11). As HIV infection progresses the degree of viremia increases, the percentage of infected CD4+ T cells increases (Figure 1) and the absolute number of CD4+ T cells drops (12-14) (Table 2). The absolute number of peripheral blood CD4+ T cells correlates strongly with the degree of clinical immunodeficiency (15) (Figure 2). Taken together these observations suggest that the immune deficiency of HIV infection is <u>directly</u> related to altered T helper function.

Table 2
Change in the CD4 Cell Count in Prospectively Followed Patients with CDC Class II, III, and IVa Infection, According to the Results of Serial Assay of Plamsa for HIV

Culture Result (No. of Patients)	Median Time between Samples	CD4 Count		Mean Proportional Decline per Month of Follow-up
		1st sample	2nd sample	
	mo	*mean (±1 SD) no. cells/μl*		*percent*
Negative in both samples (n = 7)	11.7	705±302	619±205	−0.8
Negative in first, positive in second (n = 8)	6.3	446±162	331±159	−3.5
Positive in both samples (n = 7)	2.3	284±93	224±150	−8.4

N. Engl. J. Med. 321:1629, 1989

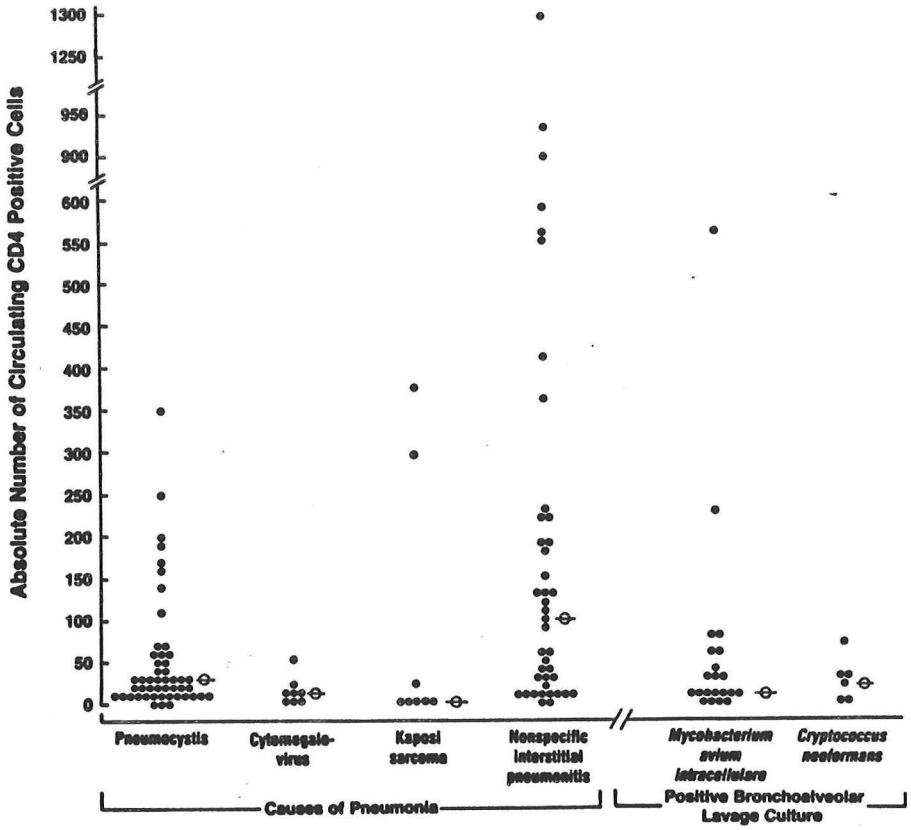
Figure 1



Titers of infectious HIV-1 in plasma and PBMC of 22 control subjects and 54 patients in different stages of HIV-1 infection. HIV+ denotes asymptomatic seropositive patients; ARC, patients with the AIDS-related complex; AZT, patients receiving long-term zidovudine treatment; and PBMC, peripheral-blood mononuclear cells.

N. Engl. J. Med. 321:1623, 1989

Figure 2



Circulating CD4 counts determined within 60 days of pulmonary diagnosis for 119 episodes of pulmonary dysfunction in 100 HIV-infected persons. Each solid circle represents one episode of pulmonary dysfunction. The open circle represents the median CD4 count.

Ann. of Intern. Med. 111:224, 1989

When appropriately stimulated by a macrophage or another accessory cell, CD4 lymphocytes proliferate in response to foreign antigen. In the process of proliferation CD4 lymphocytes 1) provide help to B cells for the production of immunoglobulin, 2) provide help to cytotoxic/suppressor CD8+ lymphocytes, 3) release lymphokines capable of upregulating the immune function of mononuclear phagocytes, 4) differentiate to provide effectors for delayed type hypersensitivity. Thus CD4 lymphocytes potentially impact on a broad range of immune functions.

In human lung the function of CD4+ lymphocytes appears to be tightly regulated. The alveolar compartment, where most infectious proceses in AIDS patients occur, is normally underpopulated with CD4 cells compared to blood. While 30-50% of mononuclear cells in blood are CD4+ lymphocytes only 3-4% of mononuclear cells in the alveolus are T helper cells (16). In HIV-infected patients a lymphocytic alveolitis composed of CD8+

cells may occur (Table 3). Early in the course of infection CD8+ D44+ HIV specific cytolytic T lymphocytes have been observed (17). In the latter stages of disease CD8+ Leu7+ suppressor lymphocytes are common and may contribute to a down-regulation of immune function (18). However the absolute CD4 count in bronchoalveolar lavage (BAL) remains in the normal range until the late stages of the disease (16,19). Alveolar macrophages (AM), the predominant immune cell in the alveolus, are normally highly suppressive of a variety of T helper functions including proliferation and cytokine release (20-22). Thus the alveolus normally has comparatively few T helper cells and the function of these cells is largely suppressed. This would suggest that the mechanism by which T helper cell depletion produces an immunodeficiency state in the lung is likely to be subtle and may differ from other organs. There is little evidence of spontaneous CD4+ lymphocyte proliferation or help to B cells occurring normally in the alveolus. Therefore these components of CD4 function are unlikely to contribute significantly to the local immunodeficiency in AIDS patients.

Table 3
ABSOLUTE NUMBER (CELLS X 10^3/ml) OF BAL LYMPHOCYTES

	CD3+ (T CELLS)	CD4+ (HELPER)	CD8+ (CYTOTOX/SUP)
NORMAL	7.1	4.9	2.5
HIV+	20.4*	3.1	17.7*

*P<0.05 VERSUS NORMAL CONTROLS

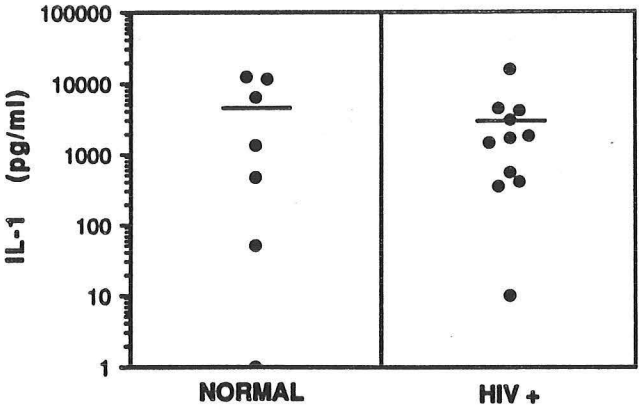
Am. Rev. Respir. Dis. 138:1609, 1988

The ability of CD4+ lymphocytes to release cytokines such as interferons or interleukin-2 (IL-2) may be important to the immune function of macrophages. The ability of macrophages to kill intercellular micro-organisms (such as M. tuberculosis) and growth inhibit some extra-cellular pathogens (such as C. neoformans) depends on the activation of macrophages by lymphocyte products (23,24). However, other lymphocytes (most notably CD8+ cells and natural killer cells) may also release these cytokines.

Although the function of lung macrophages in AIDS patients is a subject of ongoing research, several recent studies have suggested that a gross defect in AM activation does not exist. Indeed AM from AIDS patients have been reported to demonstrate equal or enhanced release of interleukin-1 (Figure 3) (25,26), tumor necrosis factor (27), and enhanced accessory cell function (Figure 4) (26) compared to normal AM. Despite these studies

clinical findings of macrophages heavily laden with mycobacteria in patients with disseminated MAI suggest that some component of activation is lacking. Recent studies have documented the feasibility of delivering nebulized gamma-interferon to the lower respiratory tract (28) in dosages sufficient to activate macrophages. Thus re-constitution of deficient macrophage activation is theoretically possible.

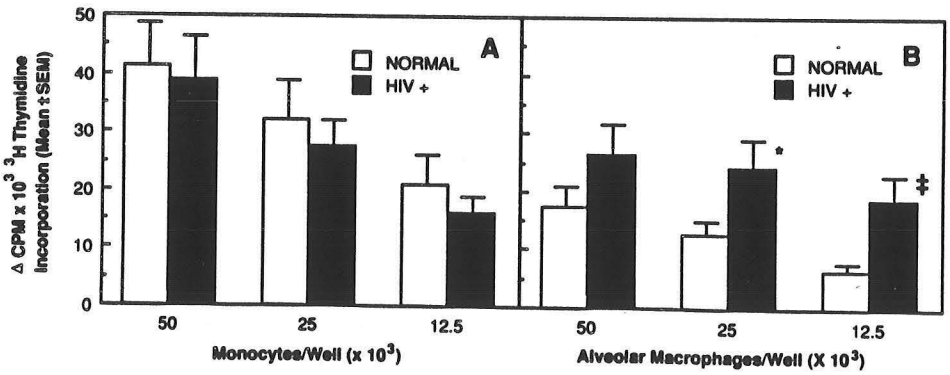
Figure 3



Antigenic IL-1 production by LPS-stimulated AM from normal volunteers and HIV-positive patients. Supernatants were assayed for IL-1 ß using an ELISA.

Am. J. Respir. Cell Mol. Biol. 1:395, 1989

Figure 4



Stimulation of a Con A mitogen response by blood monocytes (A) and alveolar macrophages (B) from normal volunteers and HIV-positive patients.

Am. J. Respir. Cell Mol. Biol. 1:395, 1989

Subtle defects in AM immune function could relate to a direct effect of the virus on AM, cells which express CD4 and have been shown to harbor HIV (29). The pulmonary immune defect in AIDS patients may also involve either reduced CD4 help to cytotoxic CD8+ cells or diminished delayed type hypersensitivity. The contribution of CD4 lymphocytes to pulmonary defense against opportunistic pathogens may also differ quantitatively from that observed in other organs. Depletion of CD4 lymphocytes in a murine model of cryptococcal infection resulted in significant dissemination to brain, spleen and liver, but had a smaller effect on organism load in the lung (30).

Thus the nature of the local pulmonary immune defect in AIDS remains unclear and is likely multifactoral. However, it is still probable that altered function of CD4+ lymphocytes contributes significantly to the local immunodeficiency. The unique pattern of opportunistic infection, particularly the predominance of PCP, suggests that highly specific defects must exist. Detailed knowledge of the pathogenesis of PCP may subsequently provide a clue as to why this organism predominates.

INFECTIOUS PROCESSES

PNEUMOCYSTIS

Pneumocystis carinii (PC) is generally classified as a protozoan parasite though recent molecular studies have suggested that it more closely resembles a fungus (31). PC was initially described by Chagas in 1909 who initially confused its microscopic appearance with that of Trypanosoma cruzii. Infection in humans was not documented until 1938 but became epidemic amongst malnourished newborns in post-World War II Europe. Prior to the appearance of AIDS the major experience with PC occurred in children undergoing chemotherapy for hematologic malignancies.

The natural habitat of PC is unknown but clinical disease in humans is thought to represent re-activation of latent infection (32). Antibodies to PC are found in 50% of children age 4 (33). These antibodies are not protective against PC pneumonia (PCP) but may function as opsonins (34,35). Cellular immunity is thus believed more crucial in defense against PC than is humoral immunity. PCP occurs in patients and animals receiving steroids (36), cytotoxic drugs (37), in T cell deficient mice (athymic nude mice) (38), and in the setting of severe protein malnutrition (39).

PC is an extracellular pathogen that is found predominantly in the alveolus though recent reports have documented the potential for dissemination (see below). PC is usually observed as a cyst with up to 8 intracystic bodies (sporozoites) present. Sporozoites are extruded from the cyst and become trophozoites. The extracystic forms (trophozoites) are more numerous and

eventually become cysts themselves. The entire life cycle occurs within 4-6 hours.

PC binds tightly to alveolar epithelium and in particular type I alveolar epithelial cells (40,41). Attachment is required for PC replication and the development of clinical disease (42). The mechanism of attachment is unknown but requires active PC cytoskeletal function and may involve mannose-containing membrane glycoproteins (43,44). Indeed recent studies have demonstrated that PC bind to fibronectin (45), a ubiquitous glycoprotein present in the alveolar space and on type 1 epithelial cells (46, 47).

The importance of attachment of PC to epithelial cells may be two-fold. First it may render the organism less susceptible to cellular defense mechanisms. Alternatively PC (which has poorly developed mitochondria) may utilize epithelial cell products as nutrients, although fusion between PC and epithelial cell membranes does not occur (48,49).

PCP is usually seen only in AIDS patients with a severe diminishment of $CD4_3$ lymphocytes. Individuals with absolute CD4 counts below $200/mm^3$ are at particular risk for clinical disease (50). It should be remembered, however, that these individuals also experience a profound HIV-1 viremia (12-14). As such the possibility exists that PCP relates to direct HIV induced changes in alveolar epithelial cells or other immune effectors.

CLINICAL PRESENTATION OF PCP

Whether the incidence of PCP in AIDS has changed in the past few years is uncertain. However, it is clear that the incidence of PCP in patients ultimately undergoing bronchoscopy has decreased (Table 4). Early series of AIDS bronchoscopies (1980-83) generally reported an incidence of PCP in excess of 85% (51). The trend towards empiric therapy for PCP both acutely and as prophylaxis no doubt has contributed to a decline in diagnosis. A series from San Francisco in 1986 reported PCP in only 57% of patients (52) undergoing bronchoscopy. At Parkland Hospital in 1985 roughly 90% of AIDS patients were found to have PCP. This has declined yearly with only 50% of AIDS bronchoscopies in 1989 showing PCP. Although this decline could truly represent a change in the overall incidence of PCP, selection bias is a more likely explanation.

Table 4
DIAGNOSIS OF PCP ON BRONCHOSCOPY

SITE	YEAR	PCP
Multicenter	80-83	85%
San Francisco	85-86	57%
Parkland	85	89%
Parkland	87	64%
Parkland	89	50%

The clinical presentation of PCP in AIDS patients is distinct from that in other types of immunocompromised hosts. Although PCP may present as an acute illness in post-chemotherapy settings, in HIV infected individuals a subacute course (3-4 weeks) is most common (53). The presenting complaints of cough and dyspnea on exertion or decreasing exercise tolerance predominate (5). Physical examination may be largely unrevealing although the presence of oral thrush (50) correlates with an increased risk of PCP. Rales have been reported in a minority of PCP cases (54). Ultimately in an HIV+ individual the clinical suspicion for PCP is determined by results of chest roentgenogram and laboratory studies.

The majority (90%) of patients with PCP demonstrate bilateral parenchymal infiltrates (55) although unilateral disease is well described. Pleural effusions or mediastinal or hilar adenopathy from PCP alone is distinctly unusual and suggests the likelihood of mycobacterial, fungal, or neoplastic disease. In some series 5-10% of patients with PCP have a normal CXR on presentation and thus a normal roentgenogram does not exclude the diagnosis (56).

Laboratory evaluation is remarkable for an elevated lactate dehydrogenase (LDH) and the magnitude of elevation correlates with disease severity (57). Hypoxemia may not be present at rest (58). However, a simple two-step exercise test (59,60) may be conducted at the bedside and a widening of the alveolar-arterial (A-a) O_2 gradient after exercise is consistent with PCP. A normal A-a gradient excludes the diagnosis for practical purposes (Table 5). Similarly, measurement of the lung diffusion capacity (D_LCO) is abnormal in PCP and a normal (>80% predicted) D_LCO largely excludes PCP (54). These tests are nonspecific and usually confirmatory of the clinical impression in patients with abnormal roentgenograms. Their value lies largely in evaluating HIV+ patients with cough, dyspnea, and a normal CXR. Gallium lung scanning has also been utilized in the presumptive diagnosis of PCP (61,62). It is highly sensitive but non-specific, expensive and appears to offer no benefit over post-exercise blood gases or a D_LCO (63).

Table 5
Screening Tests for PCP

	EXERCISE TEST	RESTING (A-a) O_2	D_LCO	CXR
Sensitivity (%)	100	71	94	74
Specificity (%)	36	35	27	30

Amer. Rev. Resp. Dis. 139:1343, 1989

DEFINITIVE DIAGNOSIS OF PCP

The common occurrence of PCP, its response to therapy and a wish to avoid invasive diagnostic tests has led to wide utilization of empiric therapy without a tissue diagnosis. Less invasive tests such as examination of induced sputum for PCP have also gained acceptance and have a published yield of 60-80% (64-66). Recently, direct and indirect immunofluorescent antibodies to PC have been utilized in the evaluation of sputum and BAL (64). These tests appear highly sensitive (92%) but their value is unproven as residual organisms are demonstrated on bronchoscopy in 1/3 of patients with PCP who are clinically well after completion of therapy (65,66).

The role of induced sputum in patient management is unclear. A negative sputum for PCP has a negative predictive value of approximately 60% (66,66a). Thus the false negative rate is high enough that empiric therapy for PCP is still indicated for most patients on initial presentation. Conversely, given the declining incidence of PCP found on bronchoscopy the yield of sputum in patients who have failed empiric therapy is likely to be low.

Bronchoscopy can be performed safely in most patients with PCP although the risk of respiratory compromise in severely hypoxemic patients (PO_2<60) is significant (67). Previous studies have suggested that bronchoalveolar lavage (BAL) alone has a yield of 85-90%, slightly lower than the yield of BAL plus a transbronchial biopsy (68). Whether the sensitivity of BAL has declined disproportionately as the overall yield for PCP has dropped is unknown. Indeed the validity of bronchoscopy as the "gold standard" for diagnosing PCP in the age of prophylactic Pentamidine and empiric therapy is uncertain and should be re-evaluated.

The decision to perform bronchoscopy for diagnosis of PCP is highly individualized. Given the continued frequency of this organism as a pathogen and its responsiveness to therapy it is likely that treatment for PCP is indicated in any hypoxemic HIV+ individual with a low CD4 count. The utility of bronchoscopy in AIDS patients may thus have more relevance for diagnosis of entities other than PCP.

THERAPY FOR PCP

Several changes in the therapeutic approach to PCP have occurred in the last decade. Although the standard of therapy remains either Bactrim or Pentamidine the route of administration and the dosages of these drugs has evolved.

Aerosolized Pentamidine (Pentam) is now widely utilized for prophylactic therapy because high levels of the drug can be achieved in the lungs with low systemic absorption (69). The therapy appears to be well tolerated except for bronchospasm

which can be blocked by pretreatment with inhaled B-agonists (70). A dose of 30-60 mg delivered by ultrasonic nebulization once or twice a month has resulted in a marked decrease in the incidence of clinical PCP compared with historical controls (70a). Preliminary results from a prospective, randomized double-blind trial in Canada (71) showed a highly significant reduction in the incidence of PCP in patients receiving Pentam. Only 5/84 Pentam treated patients developed clinical PCP compared to 27/78 receiving placebo ($p < .0001$). Delivery of the aerosol must be performed using one-way exhalation valves which prevent Pentamidine from entering the ambient environment. Pentamidine has been reported to be teratogenic and some controversy exists as to whether the therapy should be given in specially contained rooms with laminar flow ventilation systems.

The widespread utilization of aerosolized Pentamidine has likely contributed to the emergence of two new clinical syndromes. First, if the aerosol is delivered to patients quietly breathing at normal tidal volume, little drug may reach the upper lobes (72). Aerosols delivering large size droplets tend to exacerbate maldistribution. Several reports have documented an increase in upper lobe PCP since the advent of aerosolized therapy (73). Secondly, dissemination of PC has now been widely reported in patients receiving aerosolized Pentamidine. Dissemination to skin, GI tract, thyroid, CNS, liver, and the arterial circulation of distal digits have all been reported (74-80).

Although several reports in the literature have advocated the use of aerosolized Pentamidine in mild to moderately severe PCP as sole therapy, there appears to be an increased incidence of treatment failure with this regimen (81,82). Systemic administration of Pentamidine remains an important component of therapy for severe PCP. Although previous dosage recommendations suggested 4 mg/kg/d, lower dosages (i.e. 3mg/kg/d) have been utilized with some success (83-85).

Bactrim (trimethoprim-sulfamethoxazole) remains the initial therapy of choice for patients with PCP without confirmed allergy to sulfa drugs. Recent studies have suggested that a dose of trimethoprim of 12-15 mg/kg/d is sufficient to produce serum trimethoprim levels between 5-8 μgm/mL (83). This level appears to be efficacious for the management of severe PCP but has a lower incidence of serious side effects, particularly leukopenia and thrombocytopenia.

Most studies comparing Bactrim with Pentamidine have suggested that the efficacy of these agents is comparable (84,85). However a recent randomized prospective study (83) found a significant survival advantage in patients treated with Bactrim (Table 6). Eighty-six percent of patients treated with Bactrim survived compared to 61% in the Pentamidine group. Although the number of patients in this study was relatively small, the design of the study was sound and until other randomized studies are

available Bactrim should be considered the initial therapy of choice. Therapy with either Bactrim or Pentamidine likely results in at least a 70% cure rate. However if a patient fails one drug and is switched to the other, only 30% of patients will ultimately respond (51).

Table 6
Outcome of Therapy for PCP

	BACTRIM (n=36)	PENTAMIDINE (n=33)	
Survived	**86%**	**61%**	**p<0.05**
A-a Gradient Normal	**DAY 7**	**DAY 15**	**p<0.05**

Ann. Intern. Med. 109:280, 1988

Toxicity from both Bactrim or Pentamidine is significant. In earlier series up to 50% of patients required a change in therapy because of an adverse reaction (51). Bactrim has a high incidence of dermatologic reactions and bone marrow suppression, but the tolerance of the medical community for these reactions appears to have increased. In the previously cited study (83) although 44% of patients treated with Bactrim developed a rash, none had therapy discontinued and none suffered more severe dermatologic disease. Similarly, although Pentamidine caused nephrotoxicity in 64% of patients and is associated with clinically significant hyperkalemia, therapy was not stopped. Whether this contributed to the poorer outcome of the Pentamidine group is unclear. However it appears that life threatening toxicity from either Pentamidine or Bactrim in AIDS patients is considerably less frequent than reported in earlier series. Other therapies such as the combination of Dapsone and trimethoprim have been shown to be as efficacious as Bactrim but to have a lower incidence of toxicity (84). Thus, for patients who develop serious toxicity on Bactrim, either Dapsone-trimethoprim or Pentamidine can be utilized.

PROGNOSIS

Overall response to either Bactrim or Pentamidine in hospitalized patients with PCP remains between 65-80% in most reported series. It is likely however that the actual figures are higher as many patients are successfully treated with out-patient therapy alone. Length of survival for patients discharged after therapy for PCP has steadily increased over the past decade (85). The impact of zidovudine (AZT) alone on survival from PCP is unclear. Previous studies have demonstrated that in patients with CD4 counts <200 the incidence of PCP in AZT-treated and untreated patients is comparable (86). More recent data (87) has demonstrated a fourfold decrease in episodes of PCP in patients receiving PCP prophylaxis plus AZT compared to AZT alone. Thus the improved outcome of PCP likely reflects a combination of

earlier diagnosis, effective anti-viral therapy (AZT), and low toxicity prophylaxis with aerosolized Pentamidine.

Despite the responsiveness of most cases of PCP, a significant percentage of patients will progress and develop acute respiratory failure. The development of acute respiratory failure with an "ARDS-like" syndrome may be rapid and carries a high mortality. Some series have reported that this syndrome occurs most frequently in a subset of patients with >5% neutrophils on initial BAL (88). Recent trends in the survival of AIDS patients with respiratory failure secondary to PCP have altered the management of these patients in many institutions (Table 7).

Table 7
Survival of Intubated PCP Patients

SITE	YEAR	% SURVIVED
Multicenter	80-83	14%
San Francisco	83-85	13%
San Francisco	86-88	40%
Cook County	87-88	36%

Studies prior to 1985 demonstrated that the survival rate for intubated patients with PCP was less than 15%. Of the patients who survived, a significant period of time was spent in the hospital, and the overall survival period was approximately 3-4 months. These findings led to a widespread belief that ventilator management for AIDS patients with PCP was not indicated. At San Francisco General Hospital the number of AIDS patients admitted to the ICU showed a sharp decline in the years 1983-1985 (89). However ICU utilization for AIDS patients began to increase in 1986 (90). The reasons for this pattern are not clear but likely reflect a number of factors capable of prolonging longevity.

Several institutions have now reported a 30-40% survival rate in intubated patients with PCP (90-92). The median survival after discharge was 7 months and most of this time was spent out of the hospital. Thus the likelihood of survival and the quality of life following survival have apparently improved. The reasons for this change, again, are unclear. No distinguishing characteristics, such as the existence of other infections or neoplasms, or recurrent PCP, have been observed in the current group of survivors compared to previous groups of intubated patients. It is also unlikely that this reflects either a "learning curve" or improved therapy against PCP. Patient selection, although difficult to quantitate, may play an important role. It is of note that despite the increase in survival statistics only 1-2 patients per month are currently intubated for PCP at San Francisco General (personal communication, P. Hopewell). Nevertheless an aggressive initial

approach to PCP with respiratory failure seems indicated in selected patients, though the identification of this subgroup remains elusive.

The use of corticosteroids as adjunct therapy in overwhelming PCP has been widely reported in anecdotal fashion (93,94). SoluMedrol (40-60 mg IV q6h) has been reported to cause improvements in oxygenation and radiographic appearance which are often dramatic. However, a prospective randomized study at San Francisco General (95) in patients with PCP and a PO_2 <60 showed no benefit in patients receiving steroids compared to placebo.

COMPLICATIONS OF PCP

In addition to an increased incidence of disseminated PCP, the development of spontaneous pneumothoraces has become an important complication in the management of PCP (96,97). Although some reports have linked this entity to the utilization of inhaled Pentamidine (98) data to firmly support this connection does not exist.

Pneumocystis is associated with a high incidence of cystic air space disease in the lung. Indeed a cavitary appearing lesion on chest radiograph in an HIV+ patient is more likely to be cystic disease from PCP than tuberculosis (see below). On plain chest radiograph, 10% of patients with PCP exhibit cystic disease (99). In many patients, the cystic disease improves with therapy for PCP although complete resolution may not occur for months. Computed tomography of the chest has been reported to disclose a 40% incidence of cystic disease in patients with PCP (100). No large series of pneumothoraces in AIDS has yet been reported in the literature and whether the outcome of these cases differs from that of other patients with spontaneous pneumothoraces is unclear.

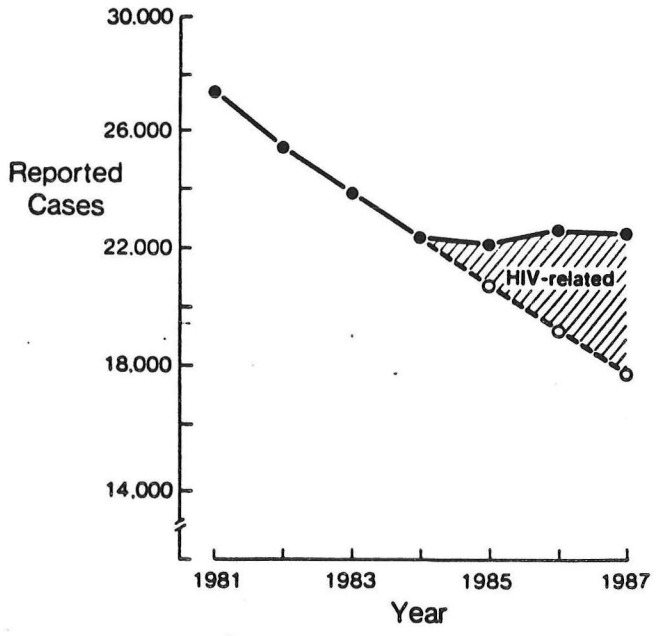
PULMONARY DISEASE FROM MYCOBACTERIA

In the first large scale analysis of pulmonary disease in AIDS patients (51) infection with mycobacterium avium intracellulariae (MAI) was documented in 17% of patients on initial bronchoscopy. However it was quickly recognized that the characteristic disease pattern in patients with AIDS and MAI infection involved the presence of disseminated disease (101). Indeed the cellular response to MAI in the lung is poor and little morbidity or mortality has subsequently been directly attributed to the presence of MAI in pulmonary parenchyma (102). These clinical observations, along with the failure of chemotherapy for MAI, have served to lessen the concern with this organism as a pulmonary pathogen in AIDS patients. The decision whether to treat patients with disseminated MAI remains controversial as it is clear that microbiologic cures are rare (101). Disseminated MAI commonly occurs in patients with CD4 counts $<100/mm^3$ and thus involves patients in the terminal stages of immunodeficiency.

In contrast to infection with MAI, increasing emphasis has been placed on the occurrence of typical tuberculosis (M.Tb.) in AIDS patients. In the above series (51) infection with M.Tb. was not documented. However, subsequent series have reported the incidence of tuberculosis infection in AIDS patients in the United States to be 4%. The incidence is higher in locations with high proportions of IV drug abusers such as New York City (5.3% incidence M.Tb.) and immigrants of Hispanic origin (Florida 8.4% incidence).

Of all the opportunistic pathogens associated with AIDS only M.Tb. can be transmitted to another individual through casual contact. As such, the diagnosis and management of TB in AIDS patients has assumed increasing importance. In 1986 a progressive 40 year decline in the incidence of tuberculosis in the United States came to a halt (102a) (Figure 5). Indeed from 1986 through 1989, the case rate/100,000 population has remained constant. Estimates by the CDC have suggested an excess 9,000 cases of TB have occurred in the United States during this time period, and that the majority of this increase is due to the development of disease in HIV+ individuals.

Figure 5



Graph showing the number of reported cases of tuberculosis in the United States from 1981 to 1987. Those that are HIV-related are shown by the hatched area.

Am. Rev. Resp. Dis. 140:1792, 1989

Data suggests that tuberculosis in HIV+ individuals is due to the reactivation of quiescent infection (Table 8). The majority of new cases of tuberculosis in an HIV+ population followed prospectively occurred in previously PPD+ individuals (103). This reactivation is likely explained by the requirement for T helper cells in the production and maintenance of a granulomatous response. The development of clinical TB in HIV+ individuals can occur at less severe levels of immunodeficiency than PCP or MAI and may prestage the development of clinical AIDS in largely asymptomatic HIV+ individuals.

Table 8
Incidence of Active TB in IV Drug Abusers
Followed Prospectively

	HIV+ (215)	HIV- (298)
Percent PPD+ on entry	23%	20%
Percent developing active TB	4%	0%
PPD+	7/8	
PPD-	1/8	

N. Engl. J. Med. 320:545, 1989

The impact of HIV infection on the epidemiology of tuberculosis has been remarkable. Analysis of all newly diagnosed cases of tuberculosis in San Francisco, Miami, and Seattle have demonstrated that 20-30% of all individuals with newly diagnosed TB are HIV+ (104). Indeed some authors have suggested that any patient with newly diagnosed TB should be tested for HIV infection. Conversely, the risk of a PPD+ individual developing clinical tuberculosis is 10 times greater in an HIV+ individual than in the HIV- PPD+ population as a whole (105). As such all patients known to be HIV+ should be skin tested for tuberculosis. Although there is a high incidence of cutaneous anergy in the late stages of the immunodeficiency, a positive skin test merits further investigation and treatment. Because infection with M.Tb. in AIDS patients is of increasing importance, it is worthwhile to review the pattern of clinical disease in these individuals.

CLINICAL PRESENTATION

The clinical presentation of tuberculosis in HIV+ individuals depends largely on the stage of immunodeficiency. In asympotomatic HIV+ individuals with normal CD4 counts, tuberculosis may present in the classical fashion of upper lobe cavitary disease, cough, fever and weight loss. However in immunocompromised HIV+ individuals, the clinical presentation of tuberculosis is distinct. While dissemination of M.Tb. is found

in 50% of AIDS patients, pulmonary infection is still proven in the majority of cases.

The radiographic pattern of infection with M.Tb. in AIDS patients is often confusing. Compared to HIV-negative individuals, tuberculosis in AIDS patients rarely produces upper lobe disease or cavitation (104a) (Table 9). Sputum AFB stains are positive in 50-70% of cases (105a,106). However, diagnosis is frequently made only upon culture of sputum and chest x-ray may be normal in up to 1/3 of patients. The sensitivity of sputum versus bronchoscopy in these patients has not been critically addressed though preliminary data suggests that sputum culture is reliable (105a,106).

Table 9
Results of Initial Pretreatment Chest Radiographs in Patients With and Without AIDS with Pulmonary Tuberculosis at Jackson Memorial Hospital, January 1, 1980 through June 30, 1983

	Pts with AIDS (n=17)	Pts w/o AIDS (n=30)	p Values
Hilar and/or mediastinal adenopathy	10(59)	1(3)	<0.001
Localized pulmonary infiltrates involving middle or lower lung field	5(29)	1(3)	<0.05
Localized pulmonary infiltrates involving upper lobes	3(18)	29(97)	<0.001
Pulmonary cavities	0(0)	20(67)	<0.001
No pulmonary infiltrates	6(35)	0(0)	<0.005

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Two important findings on chest radiograph should increase the suspicion for infection with M.Tb. First, the presence of mediastinal or hilar adenopathy in an HIV+ individual should be assumed to be tuberculosis until proven otherwise (107,108). Mediastinal and hilar adenopathy in AIDS patients is uncommon and of the entities likely to produce this pattern (M.Tb., MAI, fungal disease, lymphoma, Kaposis sarcoma) mycobacterial disease occurs most frequently. Secondly, pleural effusions are uncommon in patients infected with PCP alone (108) and the finding of a pleural effusion (especially in conjunction with mediastinal adenopathy) should raise the possibility of M.Tb. Although infection with M.Tb. tends to be chronic, rapid dissemination of M.Tb. in AIDS patients can occur. Therefore, in the opinion of the author, all HIV+ patients with pulmonary symptoms or objective findings of pulmonary disease should have sputum cultured for M.Tb. Any patient with intrathoracic adenopathy should be started on antituberculous therapy pending cultures.

THERAPY

Several regimens have been utilized for the therapy of mycobacterial disease in AIDS patients. Multidrug regimens have been utilized for treatment of non-tuberculous mycobacterial disease. The combination of INH, ansamycin, ethambutol, and clofazimine had been suggested as an improvement in standard therapy for treatment of MAI (109). However larger studies in HIV+ patients using this regimen have been disappointing (110). Most studies have suggested that even patients receiving intensive chemotherapy for non-tuberculous mycobacteria fail to respond.

Therapy for M.Tb. is usually effective in HIV+ individuals. There are no published comparisons between a two drug regimen of INH and rifampin vs. INH, rifampin and either pyrazinamide or ethambutol. However the majority of HIV+ patients with TB will respond to either a two or three drug regimen (111). The appropriate duration of treatment for HIV+ patients with M.Tb. is unknown. It is currently recommended that treatment continue for a minimum of 9 months and for at least 6 months after documented culture conversion. Roentgenographic improvement occurs in the majority of patients and a deteriorating chest x-ray in the setting of appropriate chemotherapy should suggest the presence of another infectious or neoplastic process. All patients who are HIV+ and PPD+ should currently be treated with INH chemoprophylaxis. The optimum duration of this therapy is unknown but current recommendations suggest that at least one year of therapy is prudent.

FUNGAL DISEASE

Fungal pneumonias comprise less than 10% of all cases of pulmonary disease in AIDS. However, response to therapy often occurs and as such the exclusion of a fungal process in a patient who fails to respond to therapy for PCP is of importance. Infection with several fungi including histoplasmosis, cryptococcus neoformans, coccidioidomycosis, and blastomycosis have been reported in HIV+ individuals. Infection with these organisms frequently involve sites other than the lung, although the portal of entry is believed to be the respiratory tract (112,113).

Histoplasmosis is an intracellular organism and the propensity for the development of this infection in HIV+ individuals likely pertains to altered macrophage function as a result of decreased T help. The clinical presentation of histoplasmosis in AIDS patients includes fever, lymphadenopathy, splenomegaly, cough and pulmonary infiltrates (114). Infiltrates are usually nodular and bilateral. The disease has been well described amongst AIDS patients in areas where histoplasmosis is not endemic (115).

Published series suggest that bone marrow biopsy yields a diagnosis in 50-70% of patients. Pulmonary involvement varies among series, but appears to be present in 25-33% of cases. Bronchoscopy is reported to yield a diagnosis in 87% of patients overall. Examination of histopathologic specimens with identification of the yeast has been reported in 70% of cases and granulomas have been described in 60% of individuals.

Response to Amphotericin B in patients with histoplasmosis is variable. Mortality is essentially 100% in patients who receive less than 500 mg Amphotericin B (114). Even those individuals who receive a higher dose have a 50% mortality. Although response to therapy may occur initially, relapses are frequent. Chronic suppressive therapy with ketoconazole has been advocated following initial therapy with Amphotericin B. The efficacy of this therapy is unclear although some published reports suggest an improved survival in patients on ketoconazole (116). No studies in the literature are available to evaluate the role of fluconazole, a new and more potent oral antifungal agent. At autopsy even patients who have received adequate therapy with Amphotericin have a high incidence of disseminated histoplasmosis involving the reticuloendothelial system, adrenal glands, kidney, pericardium, and gastrointestinal tract.

Cryptococcus neoformans is a ubiquitous organism which can produce both pulmonary and systemic disease. Cellular defense against cryptococcus is believed to involve both phagocytic and lymphoid effectors (117,118). Cryptococcus has been reported in 2-4% of AIDS patients. The majority of these patients present with central nervous system infection and the majority of these do not have pulmonary involvement (112). Clinically significant pulmonary infection is diagnosed in approximately 20% of AIDS patients with cryptococcus infection. The chest roentgenogram is often non-specific, although adenopathy is common (105). Diagnosis of pulmonary C. neoformans is made almost exclusively by bronchoscopy (112). Indeed the high incidence of oropharyngeal candidiasis renders fungal culture of sputum in AIDS patients largely pointless.

Therapy for cryptococcal disease with Amphotericin B appears to be effective although prolonged maintenance suppression therapy is often required. Clinical relapse was observed in 50% of patients treated with Amphotericin B without maintenance therapy and in no patients given chronic suppressive Amphotericin B (119). Maintenance doses of Amphotericin B range from 0.7-1.5mg/kg of body weight (119) per week. The recent development of fluconazole will likely alter the therapy for cryptococcal disease in AIDS patients. Preliminary experience with this drug suggests that it is an effective agent for cryptococcal meningitis and is superior to ketoconazole. Prospective studies will be necessary to determine whether similar efficacy exists for pulmonary infection.

BACTERIAL INFECTIONS

In addition to opportunistic pathogens AIDS patients can develop pulmonary infection with aerobic bacterial organisms. Several reports have demonstrated an increased incidence of bacteremia in AIDS patients with pneumococcal pneumonia compared to non-HIV infected individuals (120-122). Recurrent pneumonias with the same organism have been reported and these are largely encapsulated organisms such as pneumococcus or H. influenzae. Recurrent infection likely reflects an alteration in humoral immunity with a diminished capacity to produce de novo antibody secondary to a loss of T cell help.

Recent attention has focused on an increased incidence of community acquired pneumonia with staph aureus in HIV+ patients who were not IV drug abusers (123). Clinical presentation is similar to all community acquired pneumonias with an acute presentation characterized by fever and productive cough. Physical signs of pneumonia are present in all patients and chest roentgenogram is characterized by focal infiltrates (124). The overall significance of staph as a pulmonary pathogen in AIDS is unclear. However any HIV+ individual whose clinical presentation suggests a bacterial pneumonia should receive appropriate anti-staphlococcal coverage.

Several cases of infection with Rhodococcus equi have been reported at Parkland and other institutions (124,125). R. equi is an aerobic gram positive bacteria which characteristically produces cavitary disease in the upper lobes with associated pleural thickening. The organism is resistant to pencillin and most cephalosporins but responds to either erythromycin or Bactrim. Although this organism is rare it should be included in the differential diagnosis of a cavitating lobar pneumonia in HIV+ individuals.

NON-INFECTIOUS PROCESSES

INTERSTITIAL PNEUMONITIS

Two forms of interstitial pneumonia have been described in HIV+ individuals. Lymphoid interstitial pneumonitis (LIP) has been predominantly described in children. It is characterized by the accumulation of lymphocytes, predominantly CD4+ cells, in the pulmonary interstitium (126).

LIP had been described prior to the onset of the AIDS epidemic and is likely to reflect a variety of etiologies. In HIV-infected individuals evidence suggests that the lymphocytic response may be directed against HIV itself. The frequency of cells containing HIV RNA in an infant with LIP was significantly higher than that of bronchoalveolar lavage cells in patients with AIDS and someother pulmonary disease (127). However other viral nucleic acids, most notably Ebstein-Barr virus, have been

isolated from these specimens (128) and the etiology of LIP remains unknown.

The majority of cases of LIP have been described in children and, indeed, a diagnosis of LIP in a child under 13 years of age who is HIV+ is adequate for a diagnosis of AIDS. Chest roentgenograms usually show bilateral infiltrates and adenopathy may be present (129). Diagnosis is usually not established by transbronchial biopsy and thus is often made clinically. The course of LIP is variable and progression to respiratory failure or spontaneous resolution may occur. Some studies have suggested a response to corticosteroids though there is a high spontaneous improvement rate (120).

LIP is uncommon in HIV-infected adults though it was described in 3% of patients in New York (130). A high correlation between LIP and lymphocytic infiltration in the parotid and salivary glands, bone marrow, and liver has been reported. The clinical presentation of LIP in adults is similar to that of PCP in that it is of insidious onset and characterized by cough and fever. Clinical diagnosis may be suspected by the presence of a lymphocytosis and hypergammaglobulinemia. Anecdotal reports of response to steroid therapy exist though spontaneous resolution of LIP in adults has also been reported (131,132).

NON-SPECIFIC INTERSTITIAL PNEUMONITIS

Non-specific interstitial pneumonitis (NIP) is largely a diagnosis of exclusion characterized by a mild mononuclear cell infiltration on transbronchial biopsy. In some series the frequency of diagnosis of NIP has been as high as 38% (133). The clinical presentation is similar to that of LIP and other opportunistic infections in AIDS patients. The prognosis of non-specific pneumonitis is apparently better than that of LIP, and resolution without specific therapy is often the case (133).

KAPOSIS SARCOMA

Kaposis sarcoma (KS) is the most common malignancy in patients infected with HIV (134). In early series 50% of AIDS patients in New York City had a diagnosis of KS. However, this had declined to 30% in 1987 and a further decline continues (135). The overall frequency of pulmonary involvement by KS is uncertain as an open lung biopsy is usually necessary to definitively establish the diagnosis. Pulmonary involvement in patients without cutaneous KS is uncommon but has been reported (136,137). Pulmonary involvement with KS at autopsy has been documented in approximately half of patients with KS (138,139) and is responsible for respiratory symptoms during life in approximately 33% (140).

The clinical presentation of pulmonary KS usually involves dyspnea, cough, and fever. However many of these patients may

have co-existing pulmonary infection with opportunistic pathogens. Hemoptysis occurs in some patients and likely represents parenchymal bleeding from highly vascular KS lesions. Hemoptysis is uncommon with other processes in AIDS and thus the presence of hemoptysis should raise a suspicion of pulmonary KS.

Chest roentgenogram may offer major clues to the diagnosis of pulmonary KS. Although parenchymal involvement may be either diffuse or focal, the predominant pattern is that of diffuse linear densities which follow septal lines (141). Nodular infiltrates of varying sizes are also common (142, 142a). In some patients a lobar infiltrate secondary to a post obstructive pneumonitis may be seen. Pleural effusions are a common radiographic finding as is intrathoracic adenopathy. Some recent reports have suggested that computed tomography which documents unsuspected endobronchial lesions in an AIDS patient is highly specific for a diagnosis of pulmonary KS (141).

Diagnosis of KS is usually not made on a bronchial biopsy as KS may be located deep in the submucosa and is thus inaccessible to the biopsy forceps. In most institutions the characteristic appearance of slightly raised, violacious papules is sufficient for making a diagnosis of KS. However the absence of endobronchial lesions does not exclude parenchymal KS (140-142). Although there are some reports in the literature suggesting excessive bleeding following transbronchial biopsy in patients with KS, overall the procedure apppears to be well tolerated though rarely diagnostic (143). Despite the fact that pleural effusions are common in pulmonary KS pleural biopsy has been uniformly fruitless in making this diagnosis (140,142). Good responses to therapy have been reported in 30% of patients with KS treated with interferon-alpha in combination with chemotherapy. Patients who respond to therapy have a median survival of 10 months vs. a survival of 6 months for non-responders (144).

LYMPHOMAS

The frequency of non-Hodgkin's lymphoma is increased in HIV+ individuals (145,146). Thoracic involvement may occur and has been reported in up to 25% of patients in most large series (147,148). However the major presenting features of lymphomas in AIDS patients usually do not relate to the chest. The chest roentgenogram usually shows both parenchymal and nodal disease (130). Pleural effusions may occur and can either be unilateral or bilateral (149). Diagnosis is usually established by an open nodal or lung biopsy.

Hodgkin's disease occurs infrequently compared to non-Hodgkin's lymphoma but may involve the chest in HIV-infected individuals (150,151). Parenchymal disease is less common than in non-Hodgkin's lymphoma. Although the presence of adenopathy should raise the possibility of lymphoma in an HIV-infected individual other etiologies such as mycobacterial or fungal

infection are far more frequent. Intrathoracic adenopathy should never be ascribed to the peripheral lymph node syndrome (ARC) and always implies either active infection or a malignancy (107,108).

SUMMARY

Several major changes in the pattern of pulmonary disease in AIDS patients have occurred over the past decade. Pneumocystis carinii remains the most common pathogen causing pulmonary disease though its incidence has declined and the reliability of bronchoscopy to document this infection in patients receiving prophylactic Pentamidine is uncertain. Overall, trends in HIV-infected individuals with pulmonary disease are positive. Infection with mycobacteria tuberculosis has emerged as a major public health problem in HIV+ individuals and in some third world countries has reached crisis proportions. Because the prognosis of HIV-infected individuals with pulmonary disease directly relates to the degree of immunodeficiency, it is likely that further strides in understanding the pathogenesis of AIDS will greatly improve the current level of survival. Continued development of effective anti-viral therapies and the utilization of such therapies prior to the development of an immunodeficiency state will likely have a major impact on the course of pulmonary disease in AIDS patients in the future.

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