The clinical and radiologic presentation as well as the macroscopic and histologic characteristics of lung parenchyma in three HIV-infected patients with Pneumocystis carinii pneumonia (PCP) are detailed. The distinguishing clinical feature in these patients was a prolonged stable clinical course of the disease over at least 4 to approximately 24 months. Serial chest radiographs in two patients demonstrated persistent focal radiographic lesions. In one patient blebs in both upper lobes were not recognized until thoracoscopy/thoracotomy was performed. Biopsy specimens of affected areas revealed extensive interstitial fibrosis, occasional giant cell reactions, and honeycombing. In view of the combined clinical, radiologic, macroscopic, and histologic patterns, it is suggested that these patients had a chronic productive form of PCP rather than the well-known acute presentation of the disease. Data from the literature confirm the impression that atypical histologic lesions of PCP, either of a productive or destructive nature, are frequently related to a prolonged clinical course. It is unlikely that prophylactic pentamidine contributes to this entity. Coinfection with other pathogens may have a role. Given the recent evidence on augmented release of tumor necrosis factor (TNFα) in HIV-associated pulmonary complications, it is speculated that TNFα may be of importance in producing focal fibrosis in Pneumocystis infection of the lung.

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A typical clinical and histologic presentations of Pneumocystis carinii pneumonia (PCP) have been reported in a minority of patients in the pre-AIDS and AIDS era. They are of special interest in that they (1) represent a more intense inflammatory response to the organism perhaps favoring its persistence, and (2) may be associated with a prolonged or chronic course of the infection. Herein we describe three patients in whom the diagnosis of chronic PCP was made by thoracoscopic biopsy specimen. In two of them, repeated bronchoscopic workups had been nondiagnostic. All patients had a prolonged stable clinical course associated with focal radiologic or macroscopic markers of the disease. The pertinent literature is reviewed and compared with the patient characteristics under study.

CASE REPORTS

CASE 1

A 48-year-old male homosexual with known human immunodeficiency virus (HIV) infection since 1989 noted the onset of productive cough, dyspnea on exertion, night sweats, fever, and fatigue in November 1991. He had received continuous pentamidine aerosol prophylaxis and zidovudine (AZT) since 1990. There was no history of previous PCP; other opportunistic or bacterial infectious diseases of the lung or airways. A chest x-ray film in January 1992 revealed bilateral small apical cysts and nodules highly suggestive of tuberculosis or fungal infection. Bronchoscopy was performed in January 1992. Transbronchial biopsy specimens were nondiagnostic. The lavage fluid was devoid of acid-fast bacilli or fungal elements; P carinii could not be found by immunofluorescent staining. The

**AM =** alveolar macrophage; **BAL =** bronchoalveolar lavage; **CMV =** cytomegalovirus; **MAI =** Mycobacterium avium-intracellularare; **PCP =** Pneumocystis carinii pneumonia; **TMP-SMX =** trimethoprim-sulfamethoxazole; **TNF =** tumor necrosis factor
bronchoalveolar lavage (BAL) contained the following cell percentages (our normal values are given in parentheses): 86 percent macrophages (74 to 94 percent), 13 percent lymphocytes (5 to 22 percent), 1 percent neutrophils (<1 to 4 percent), and <1 percent eosinophils (<1 to 1 percent). T-cell subsets were 2 percent for T-helper lymphocytes (22 to 74 percent) and 74 percent for T-suppressor/cytotoxic lymphocytes (17 to 44 percent). Despite subsequent antituberculous therapy for 2 months, his clinical and pulmonary status failed to improve. Radiographs of the chest obtained in February and March 1992 invariably revealed cyst-like lesions in both upper lobes (Fig 1). Blood T-cell counts yielded 10/μl T-helper cells and 220/μl T-suppressor/cytotoxic cells. At the time of hospital admission, the patient had low-grade fever and was mildly anemic (3.3 × 10^9 red blood cells per microliter [4.3 to 5.7]). The white blood cell count was 2,400 cells per microliter (3,800 to 10,500) with a normal differential. Serum lactate dehydrogenase was 227 U/ml (140 to 290). Only his IgE was markedly elevated: 714.7 IU/ml (20 to 80).

In March 1992, a right-side thoracoscopy was carried out. The visceral pleura of the lower and middle lobes was normal and so were the parietal and diaphragmatic pleura. However, the pleura of the upper lobe was covered with scattered patches of fibrous tissue or fibrin. Biopsy specimens were obtained from this region.

Histologically, the lung showed focal widening of air spaces with interstitial fibrosis reminiscent of early stages of honeycombing (Fig 2, top). Alveoli contained only a few Pneumocystis organisms with

**Figure 2.** Top left, Case 1. Overview of pulmonary changes in chronic P carinii pneumonia: persistent alveolar exudate containing P carinii organisms, marked interstitial lymphocytic infiltrate, and widening of air spaces (initial honeycombing). (hematoxylin-eosin, original magnification ×150). Top right, Case 1. Persistence of exudate and interstitial inflammatory cells is accompanied by interstitial edema and progressive production of collagen fibers (red) (Van Gieson stain, original magnification ×375). Bottom left, Case 1. The alveolar exudate contains few intact Pneumocystis organisms and masses of debris apparently from partially broken down organisms. PAP technique using monoclonal antibody against P carinii (Dako, original magnification ×600). Bottom right, Case 3. Alveolar debris and Pneumocystis organisms (deep purple) evoke a progressive interstitial inflammatory response with resorptive giant cell formation (periodic acid-Schiff reaction, original magnification ×600).
exudate and more abundant debris. The debris stained positively with monoclonal antibodies against *P. carinii* and therefore probably consisted of breakdown products from the organisms (Fig 2, bottom left). There was only a mild interstitial lymphocyte infiltrate and focal resorptive inflammation revealing accumulations of macrophages without classical granuloma formation.

The patient was treated with trimethoprim-sulfamethoxazole (TMP-SMX) and had complete resolution of fever, cough, shortness of breath, night sweats, and fatigue within 3 weeks of therapy. Both upper lobes were radiologically clear.

**CASE 2**

A 29-year-old heterosexual woman with atopy in early childhood presented to her physician in January 1991 complaining of productive cough and occasional mild attacks of breathlessness. The lungs were clear on auscultation and radiographs of the chest were normal. Spirometry revealed mild airway obstruction. Skin tests gave positive responses to pollens from trees and grasses, and to house dust and cats. A diagnosis of allergic bronchial asthma was made. The treatment regimen consisted of inhaled steroids on a regular basis and β-mimetics on demand. The steroids were used from April through November 1991 but the patient reported no improvement in her pulmonary status.

In October 1991, bacterial pneumonia was assumed, and the patient was treated with a 14-day course of antibiotics. No definite improvement ensued. In November 1991, a chest radiograph revealed reticulonodular infiltrates in both lower lung fields. Subsequent bronchoscopic biopsy specimen showed patchy lymphocytic infiltration of the alveolar septae. No granuloma or fungi were found. Stains for *P. carinii* were not performed. In view of the patient's clinical and radiologic presentation, a tentative diagnosis of hypersensitivity pneumonitis was made. A 4-week course of prednisolone (40 mg/d) was administered with subsequent clinical deterioration.

In February 1992, she presented to another pulmonary physician with continuing exertional dyspnea and respiratory wheeze. Repeated bronchoscopy was nondiagnostic for fungi, acid-fast bacilli, and other pathogens. Again, special stains for *P. carinii* were not done. The BAL fluid was reported to contain 10 percent macrophages, 6 percent lymphocytes, 78 percent neutrophils, and 6 percent eosinophils. Serum IgE-antibody titers to usual allergens such as microspora faeni, thermoactinomycetes, aspergilli, and penicilium were normal. The serum was positive for HIV antibodies. In view of her chest radiograph with persistent interstitial markings and fluffy infiltrates in both lower lung fields and the then documented cellular immunosuppression with peripheral blood counts yielding 69/µl T-helper cells and 982/µl T-suppressor/cytotoxic cells, the diagnosis of hypersensitivity pneumonitis was dismissed. Antituberculous treatment was begun.

In March 1992, she was admitted to our hospital for the first time complaining of continued breathlessness on mild exercise. The patient was afebrile. Her red blood cell count was normal. She had no leukocytosis or blood eosinophilia. The serum IgE (33.06 IU/ml) and lactate dehydrogenase (253 U/L) levels were in the normal range. Spirometry revealed severe obstructive disease with associated restriction partly reversed by 2 mg of inhaled salbutamol. A chest radiograph showed localized infiltration of the lingula and right lower lung fields (Fig 3). Transbronchial biopsy specimens were nondiagnostic. Differential counts of the BAL yielded 61 percent macrophages, 17 percent lymphocytes, 17 percent neutrophils, and 5 percent eosinophils. T subsets were 3 percent T-helper cells and 91 percent T-suppressor/cytotoxic cells. In a sample of the lavage fluid scattered oocytes were observed, but contamination of the probe with nearby positive controls could not be excluded. Again acid-fast bacilli were not detected. On thoracoscopy the surface of the left lung was macroscopically unremarkable. However, there was no complete collapse as is usual during this procedure, arguing in favor of reduced compliance due to interstitial fibrosis. Biopsy specimens were taken from the lingula. Histologically, the lung showed a moderate thickening of interalveolar septae with focal and diffuse lymphocytic infiltrate and initial fibroblast proliferation. Partially distended alveoli contained foamy and proteinaceous exudate with many *Pneumocystis* organisms. In addition, there was granular debris from these organisms as in case 1 and a focal foreign-body giant cell reaction. Fibrosis of interalveolar septae was accompanied by alveolar cell proliferation. HIV-associated lymphocytic pneumonitis was considered but was rejected in view of the presence of *P. carinii* organisms. No histologic changes suggesting lymphocytic bronchiolitis or Churg-Strauss disease were observed. Since the patient exhibited skin allergies to antituberculous drugs and TMP-SMX, an investigational antipneumocystis compound was chosen in addition to medium dose oral steroids. She had a fairly good but transient clinical and radiologic recovery after a 3-week course of 566CSO. There was less dyspnea and cough for 2 weeks and partial resolution of the infiltrates. Her final recovery was delayed by subsequently intervening pulmonary mycosis. In view of her obstructive airway disease, no pentamidine inhalation was prescribed.

**CASE 3**

Human immunodeficiency virus infection was diagnosed in this 24-year-old male hemophiliac in 1986. Four years later he had his first episode of PCP. The disease was successfully treated with TMP-SMX. Subsequently he inhaled prophylactic pentamidine and took AZT. In April 1992, a spontaneous right-sided pneumothorax was diagnosed. Apart from acute respiratory distress when tension developed, there was no history of recent dyspnea. A thoracostomy tube was placed but no medication was given in view of an otherwise normal chest radiograph. He was transferred to our hospital in early May. At the time of hospital admission, the patient had low-grade fever with intermittent bouts of high temperature. His blood revealed 20/µl T-helper cells and 410/µl T-suppressor/cytotoxic cells. He was severely anemic with RBC of 2.6 x 10^10 cells per microliter. The WBC count and differential cell count were normal. Serum lactate dehydrogenase was elevated to 344 U/mL. On the third day, an additional left-sided pneumothorax developed. A thoracoscopy was performed on this side. The collapsed upper lobe revealed occasional small blebs protruding from an otherwise smooth surface (Fig 4). The lower lobe, thoracic wall, and diaphragm
nancy, Weber et al demonstrated granulomas, multinucleated giant cells, fibrosis, and areas of calcification adjacent to P carinii organisms. However, since the patients had been pretreated with multiple chemotherapeutic regimens, cytotoxic drugs may have contributed to the parenchymal defect.

Focal productive lesions (histiocytic “granulomas,” interstitial fibrosis, calcification) were the main histologic finding in AIDS-related PCP as reported by Masur et al, Barrio et al, Bleiweiss et al, Birley et al, Lee and Schinella, and Srivatsa et al. In these 20 patients, only 2 had received prophylactic pentamidine, none AZT; 8 of 20 had previous episodes of PCP with disease-free intervals of 3 to 4 months, where specified. The duration of symptoms from onset to presentation ranged from 1 to 2 weeks. Concomitant pathogens found in lung tissue and BAL were Mycobacterium xenopi (n = 1), Mycobacterium avium-intracellulare (MAI) (n = 1), cytomegalovirus (CMV) (n = 2), Aspergillus (n = 1), and Cryptococcus (n = 1), but radiologic changes cleared with appropriate TMP-SMX therapy alone. In retrospect, we would prefer to term these presentations “chronic persistent PCP” in view of recurrent disease in many and the benign prognosis. However, owing to incomplete follow-up data in these studies, there is no definite clinical proof of chronicity in every patient.

Mainly focal destructive (cavitary) lesions often proceeding to diffuse infiltration in AIDS-associated PCP were reported by Barrio et al, Fincus et al, Eng et al, Bleiweiss et al, and Liu et al. None had received previous pentamidine aerosol, and one of these six had taken AZT. One had a previous episode of PCP with a disease-free interval of 1 month. The duration of symptoms before presentation ranged from 5 days to 7 months. Concomitant pathogens or diseases were MAI (n = 1), CMV (n = 2), and lung Kaposi (n = 1). The clinical outcome was uniformly fatal. We would term these presentations “chronic progressive PCP.”

Our patients demonstrated a prolonged clinical course with no substantial deterioration over 4, 6, and 24 months. They were severely immunosuppressed. Corticosteroids given over a long period of time may have precipitated the opportunistic infection in case 2.

Serial chest radiographs revealed persisting lesions confined to discrete areas of the lung. In one patient, focal disease was not visible on chest radiograph and was confirmed only at thoracoscopy.

Tissue obtained by thoracoscopy showed markers of a mainly productive type of infection with the pathogen in place. Lung collapse in patient 3 was most probably due to rupture of apical subpleural blebs walled off by fibrotic tissue rather than to parenchymal necrosis.

Patients 1 and 2 had no prior opportunistic pulmo-
nary complications. Hence, the observed interstitial fibrosis cannot be due to a previous healed PCP lesion as has been noted in anecdotal cases.18 Patient 3 had recurrent disease after a 2-year symptom-free interval. His remarkable lack of long-standing symptoms does not necessarily preclude chronic smouldering infection, since relapsing PCP may be an acute exacerbation of a chronic asymptomatic disease.19 Hartz et al18 recently published an interesting case of chronic subclinical non-Hodgkin's lymphoma-related PCP with a single nodule on chest radiograph. Histologic evaluation of the resected nodule revealed fibrous material surrounded by a rim of granulation tissue, and minute central necrosis containing P carinii organisms. The patient was without symptoms and had a normal postsurgical recovery without specific therapy.

It is unclear why some patients with PCP establish a sustained inflammatory response to the organism.17 It is also not known why cavitation ensues in some. We18 and others19 have suggested that alveolar macrophages (AM) may be activated by pentamidine, thus stimulating local defense mechanisms. Two of our patients received prophylactic therapy. There is some evidence that upper lobe predominance or pneumothrax in PCP may be more frequent in pentamidine inhalers.20,21 However, data from the literature do not support the idea of an association between pentamidine and fibrosis, since most of the patients presenting with atypical features did not inhale the compound (see above). Moreover, results from our own institution show enhancement of surface antigen expression on AM taken from HIV-infected patients independent of pentamidine prophylaxis.22

Coinfection with other pathogens may be of importance and has been demonstrated in some of the atypical presenters. From the sputum of one of our patients (case 3), acid-fast bacilli were cultured although there was no histologic or radiologic evidence of mycobacterial infection.

It is unclear whether a high IgE level in patient 1 or the atopic disease in patient 2 facilitated interstitial fibrosis. However, since asthma is essentially limited to the airways and no proof was at hand for hypersensitivity pneumonitis, its contribution to the parenchymal defect seems unlikely.

The close proximity of destroyed cysts and fibrotic tissue observed in some biopsy specimens also suggests an effect of intracystic material on the proliferation of fibroblasts via AM. It has been shown recently that AM isolated from HIV-infected patients with PCP vigorously secrete tumor necrosis factor alpha (TNFα).23 Pneumocystis carinii appears to induce release of the cytokine independent of phagocytosis of the organism.24 TNFα is lethal to the organism25 and is cytotoxic to some tumor cell lines in in vitro experiments.26 Moreover, TNFα has been postulated to initiate interstitial fibrosis and granuloma formation in some noninfectious lung disorders through recruitment of inflammatory cells and stimulation of fibroblast proliferation.26 Therefore, TNFα may be an important factor in the induction of chronic productive PCP, though the relationship between the level of pulmonary TNFα and the histologic picture and clinical course of the disease awaits investigation.

Whatever the cause, interstitial fibrosis in response to P carinii may have walled off the organisms and thus prevented their spread through the whole lung. Fibrosis protects the pneumocysts from inhaled drugs and allows the establishment of chronic infection. It is conceivable that recurrent or chronic infection may be localized in such areas of fibrosis.3

In conclusion, a chronic fibrosing form of PCP is observed in some HIV-infected patients. We believe that the triad of long-standing symptoms, localized radiologic or macroscopic changes, and interstitial fibrosis may be the characteristic feature of chronic PCP. The diagnosis is frequently obtained only by more invasive measures than the usual bronchoscopic workup.

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