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Review article

Imaging pulmonary disease in AIDS: state of the Art

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Abstract. The spectrum of pulmonary diseases in AIDS including infections and neoplasms that affect the lungs are reviewed. Characteristic plain film and CT findings are illustrated.

Key words: AIDS – Opportunistic infections – HIV – Kaposi Sarcoma – Chest CT

Introduction

More than 30 million people worldwide are infected with the human immunodeficiency virus (HIV), the cause of the acquired immunodeficiency syndrome (AIDS). Since its recognition in 1981, AIDS has continued to evolve as a syndrome with varied manifestations [1–3]. Although great progress has been made in the prevention and treatment of opportunistic infections in AIDS and in slowing the proliferation of the HIV virus within the body, no vaccine or cure exists for AIDS [3].

Despite the absence of a cure, new treatment approaches have significantly changed the natural history of AIDS in many patients. Protease inhibitors lower the blood levels of detectable HIV virus and appear to forestall or temporarily reverse the degree of immunosuppression and overt manifestations of AIDS in some patients. Combination drug therapies including the use of zidovudine (AZT) and other antiviral agents may also slow the progression of HIV disease in many individuals.

At least in the industrialized world, significant progress has been made on another front: the treatment and prevention of opportunistic infections that complicate AIDS. Prophylactic treatments and early detection and intervention for *Pneumocystis carinii* pneumonia (PCP), tuberculosis, pneumococcal pneumonia, and some fungal infections have changed the prevalence and severity of these pulmonary infections in developed countries [2, 4–9 a].

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As a result, life expectancy for HIV-infected individuals is improving in the industrialized world, with long-term survivors increasing in number. At least in some parts of the world, AIDS has become a chronic, slowly debilitating illness, with variations in the course and tempo of the disease, rather than the fulminating illness with rapid demise that characterized AIDS at the beginning of the epidemic. For example, 51 % of HIV-positive patients in a closely followed cohort in San Francisco remain alive after 11 years [2, 9 b].

Manifestations of AIDS-related pulmonary diseases have changed over the last decade as well. PCP, once often fatal, is now frequently preventable with prophylaxis, and survivable with aggressive, early treatment. Today, fulminate PCP with respiratory failure is a much less common presentation of AIDS. Even if not prevented with prophylaxis, PCP is more often diagnosed and treated early, resulting in a marked decrease in the number of hospital and intensive care unit admissions due to this infection. Patients with PCP and AIDS are now much more likely to present subacutely, with chronic or recurrent infections as a result of treatment failures or noncompliance. Treatment of AIDS in the industrialized world has shifted from the inpatient hospital wards to an outpatient management approach.

Unfortunately, as the prevalence of some AIDS-related infections has decreased, others have emerged as increasingly dangerous public health threats. There has been a resurgence of tuberculosis as a worldwide epidemic in the last 5 years and the emergence of multiple-drug resistant strains is a particularly aminous development. The demographics of AIDS and its complications varies tremendously depending on the region of the world, and between industrialized and non-industrialized nations. In the United States, for example, while AIDS was once recognized primarily in homosexual men, it has now spread to all segments of society, with increasing numbers of patients to be found among heterosexual intravenous drug users, their partners and offspring.

Pulmonary disease in AIDS

Chest diseases continue to account for the majority of all AIDS-defining illnesses, with lung infections causing significant morbidity and mortality [2]. For the radiologist to be successful in diagnosing pulmonary disease in AIDS, he or she must use an approach that utilizes clinical information, radiographic pattern recognition and an understanding of the natural history of HIV disease [10–14]. A wide variety of infections and neoplasms cause pulmonary disease in AIDS and their manifestations may be atypical and varied. Multifactorial disease is also common. In addition, HIV disease encompasses varying degrees of immunosuppression from the asymptomatic carrier of the HIV virus to the patient with end-stage AIDS. The degree of immunosuppression correlates well with the type of pulmonary disease present. Despite the fact that few radiographic and CT findings of pulmonary disease in AIDS are specific, patterns of involvement are recognizable and highly suggestive of certain disease processes. Using radiographic patterns of disease with a knowledge of the patient's clinical presentation, CD4 count, the underlying risk factor for AIDS, and any previous drug treatments, the radiologist can narrow the differential diagnosis and often establish a most likely diagnosis [10–12, 14–16].

HIV disease causes progressive reduction in the number of functioning CD4 helper T cell lymphocytes, but it also causes deficiencies in other humoral, cell-mediated, and phagocytic functions [1]. The CD4 count, however, is a good indicator of the degree of immunosuppression. More aggressive pathogens such as tuberculosis that are normally contained by a healthy, cell-mediated immune system may cause pulmonary infections even before the diagnosis of AIDS has been established and before the CD4 count is depressed. Recurrent community-acquired pneumonias due to encapsulated pyogenic bacteria, which are usually controlled by an intact humoral defense system, may also be the first manifestation of AIDS, even before the CD4 count has dropped below normal. It is only when the CD4 count reaches and drops below 200–250 cells/mm^3 that opportunistic infections such as PCP begin to surface. As the immune system becomes more impaired and the CD4 counts drop below 150 cells/mm^3, less virulent pathogens emerge as causes of pulmonary disease including fungal organisms, cytomegalovirus and *Mycobacterium avium* complex (MAC) [1, 13, 16, 17]. At the most severe levels of immunosuppression, AIDS-related lymphomas are most often found.

Geographic location and the underlying risk factors for AIDS will significantly influence the types and causes of respiratory illnesses encountered. For example, in Africa tuberculosis is a much more common index disease of AIDS than PCP [18]. Tuberculosis is also more prevalent in intravenous drug users who are HIV-positive and in those individuals from endemic areas [19]. AIDS patients who are intravenous drug users are also more likely to present with septic emboli or recurrent staphylococcal infections, with lung abscess and empyemas than other types of AIDS patients [11, 19]. Kaposi's sarcoma, on the other hand, is seen almost exclusively in homosexual or bisexual men and their partners.

The availability of and compliance with drug therapies will also significantly affect the type and severity of pulmonary illnesses encountered in AIDS patients [19]. In the industrialized world, PCP antibiotic prophylaxis has changed not only the prevalence but also the natural history and radiographic presentations of this infection [17]. AZT, antiviral agents and newer protease inhibitors slow or reverse the deterioration of the immune system, which in turn will affect concurrent pulmonary disease. For example, AIDS patients co-infected with HIV and TB who are started on antiretroviral therapy may demonstrate initial worsening of their radiographic and clinical manifestations of tuberculosis [20].

It is important that the radiologist keep such variables in mind when interpreting radiographic and CT findings of pulmonary diseases in AIDS.

The spectrum of pulmonary infections in AIDS

Pneumocystis carinii pneumonia (PCP)

PCP remains a common cause of life-threatening pulmonary infection in AIDS. However, advances in prevention with the widespread use of prophylaxis have led to a significant decrease in the number of hospital admissions due to PCP in the industrialized world [4–9, 17, 21–24]. Recurrence rates are also lower [25–27].

Pneumocystis carinii, once classified as a protozoan, is now thought to be a type of fungus that exists in the form of a cyst or a trophozoite [23, 27]. Pneumonia occurs when the trophozoite interdicts itself with the cell membranes of type I alveolar epithelial pneumocytes, causing cell death and leaky capillary membranes. Pulmonary alveolar spaces fill with proteinaceous fluid and 'foamy' eosinophilic exudate containing trophozoites, cysts, fibrin, and sloughed epithelial cells [23, 27–29]. Surfactant production is also impaired in the process [27]. In response to the infection, type II pneumocytes multiply and attempt to repair the damaged alveolar-capillary membranes, while lung macrophages and plasma cells are recruited into the interstitial spaces causing a mild interstitial pneumonitis [28]. Eventually, lung repair results in interstitial fibrosis [23].

Intact cell-mediated immunity, including activated macrophages and CD4 + T helper lymphocytes, are critical host defenses against *Pneumocystis* infection. Once the CD4 + count falls below 200 cells/mm^3, the risk for *Pneumocystis* infection increases significantly [30, 31]. In response to the infection, mononuclear cells and macrophages release tumor necrosis factors and cytokines that cause a marked inflammatory response in the lung [31]. Humoral factors in the form of IgM and IgG serum antibodies may also play a role in the normal host and it is believed that CD4 + T helper cells both regulate cell-mediated defenses and promote B cell production of PCP-specific antibodies [31].

Whether PCP in AIDS represents reactivation of previously dormant organisms in the lung or reinfection is not known. Evidence exists for both possibilities [27, 28, 30, 31]. Seasonal and environmental factors may also affect rates of infection, with more PCP cases reported in late spring and late summer/early fall [28, 32 a, 32 b].

Clinical features of PCP in AIDS patients vary and differ significantly from presentations seen in non-AIDS patients [33]. Nonproductive cough, increasing shortness of breath, and fever are typical symptoms, but their onset in AIDS patients may be acute or subacute, developing over days to weeks to months [27]. In some cases, constitutional symptoms may predominate [26, 27]. Typical laboratory findings include elevated serum lactate dehydrogenase (LDH), decreased arterial oxygenation, widening of the alveolar–arterial oxygen gradient, and low DLCO (diffusing capacity for carbon monoxide) [27].

The diagnosis of PCP is made by identifying cysts on a methenamine silver stain or trophozoites on a Wright-Giemsa stain [31]. The organism can not be cultured. Induced sputum is often attempted as a first means of diagnosis in AIDS patients and has a sensitivity for detection of approximately 77 %. If sputum samples are negative or unobtainable, bronchoalveolar lavage may be performed and has a sensitivity of 86–97 % in HIV-positive patients [31]. Alternatively, at many institutions, AIDS patients with typical clinical and radiographic findings of PCP are treated empirically and only undergo bronchoscopy if they fail to respond to appropriate therapy or have atypical features [28]. Newer techniques such as immunofluorescent staining with monoclonal antibodies and DNA amplification are also being used to increase detection rates in sputum and lavage samples [18, 27, 28]. However, because the risk of pneumothorax appears to be higher in AIDS patients, transbronchial biopsy is rarely used in this patient population to make a diagnosis of PCP [34].

The radiographic appearance of PCP is variable, but most patients present with diffuse, bilateral, symmetric, finely granular or reticular infiltrates that may appear interstitial or more airspace in nature on plain films [26, 27, 35–37] (Fig. 1). Pulmonary infiltrates may be diffuse, perihilar, lower lobe or predominantly upper lobe in distribution. Cases of more asymmetric lung disease are also seen (Fig. 2). Pleural effusions and lymphadenopathy are not commonly seen in patients with uncomplicated PCP. Without appropriate therapy, patients with PCP may rapidly progress to respiratory failure and ARDS (adult respiratory distress syndrome [5]. With appropriate treatment, improvement usually occurs in 5–7 days [27]. Worsening of the pulmonary infiltrates during the first 24–72 h of treatment is sometimes due to lung edema rather than progression of infection because of leaky capillary membranes and volume overload from intravenous antibiotics [17, 36].

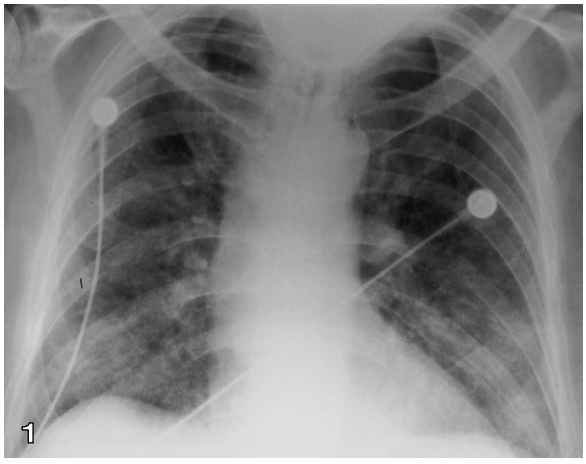
Less common presentations of PCP (5–10 % of cases) include lobar consolidation, focal lung opacities or nodules, cavities or cystic lung disease, miliary disease, endobronchial lesions and pleural effusions [13, 17, 37–41]. PCP may also present with apical infiltrates, cystic lung disease, spontaneous pneumothorax, and disseminated extrapulmonary disease [11, 35, 40, 42–52] (Fig. 3, 4). Gas-filled cystic lung lesions occur in about 10 % of patients with PCP based on chest radiographs, but are often more easily identified on CT [11, 17, 26, 35, 40, 45, 46, 48, 52–54]. Atypical presentations and cystic lesions due to PCP have frequently been reported in patients receiving aerosolized pentamidine for prophylaxis against PCP, but they can also occur without its use [26, 37, 44, 52]. With the widespread use of trimethoprim-sulfamethoxasole for prophylaxis against the infection, radiographic presentations of PCP have become more subtle. Between 10 % and 39 % of patients with documented PCP may present with a normal, near normal, or equivocal chest radiograph [35, 55–59].

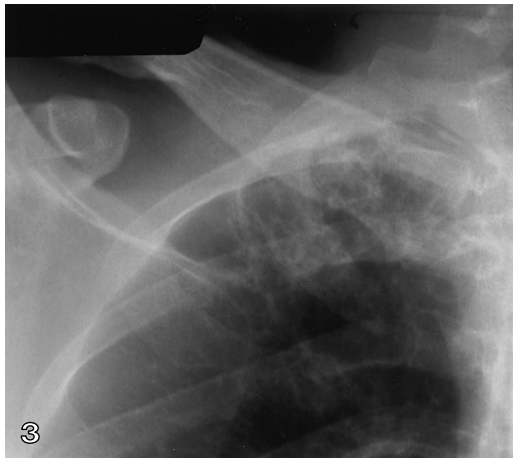
The patient with PCP may present with a spontaneous pneumothorax [60–68], estimated to occur in 6–7 % of AIDS patients with this infection [69] (Fig. 4). The likely etiology is rupture of gas-filled cysts located in the periphery of the lung [49, 52, 66, 69]. These pneumothoraces are difficult to treat and persistent bronchopleural fistulae may require chemical or mechanical pleurodesis [60–68]. PCP complicated by pneumothorax increases mortality from the infection to 33–57 %, compared with a 17 % mortality rate for those with uncomplicated PCP infection [26, 27, 69, 70].

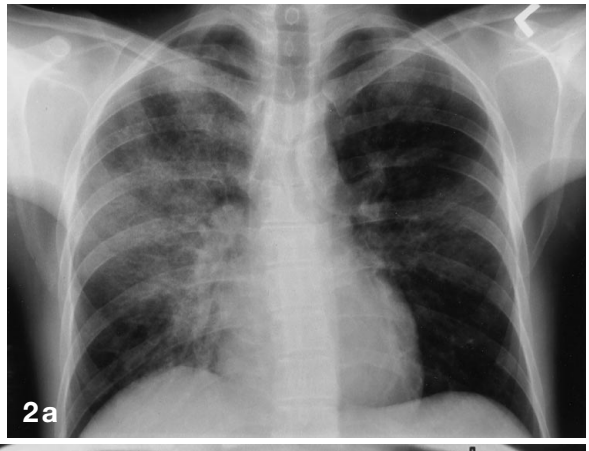
Pneumocystis infection can rarely (~ 1 % of cases) spread beyond the lungs via the lymphatics or blood stream to the lymph nodes, spleen, liver, bone marrow, skin, thyroid, adrenal glands, kidneys, and most other organ systems within the body [27, 59, 71–82]. When aerosolized pentamidine was widely used as a prophylactic treatment for prevention of PCP, many cases of disseminated PCP were recognized and it was theorized that uneven lung distribution and low systemic levels of the drug allowed for chronic infection to persist and eventually spread beyond the lungs [37, 44, 71, 72, 80, 81, 83]. An interesting feature of disseminated *Pneumocystis* infection seen on CT and ultrasound is the presence of punctate or rim-like calcifications within affected organ systems such as enlarged lymph nodes, spleen, liver, or kidneys [74, 75, 78, 84, 85]. Pleural or peritoneal surface calcifications with effusions or ascites may also be seen, as can abscesses in various intra-abdominal organs [26, 74, 75]. Pleural effusions, however, are rare in uncomplicated, non-disseminated PCP infection [26, 86].

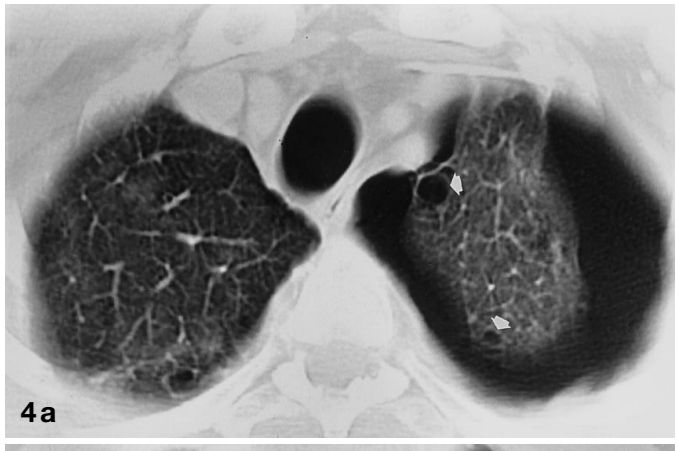
More recently, a number of airway manifestations of PCP in AIDS have been reported including symptoms of wheezing, airway hyperactivity, reversible decreases in peak expiratory flow rates, bronchiectasis on CT, and bronchiolitis obliterans on lung tissue samples infected with *Pneumocystis* [52, 87, 88].

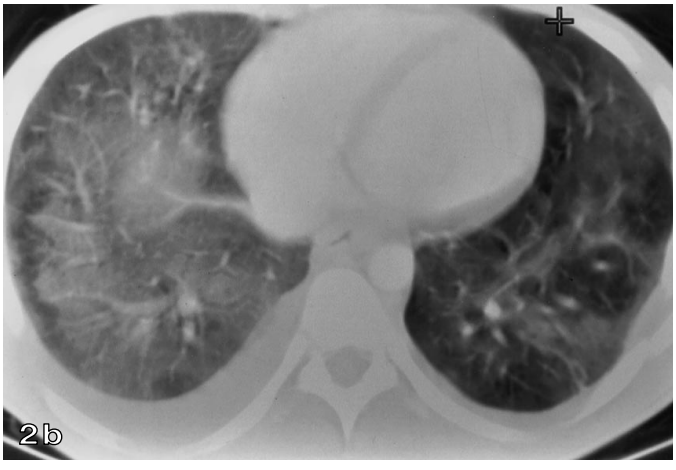
The CT findings of PCP have been extensively described and encompass a spectrum of features [14, 17, 26, 89–91] (Figs. 2, 5, 6). Characteristic features of PCP include bilateral ground-glass opacities that may be diffuse or patchy in distribution [89, 90] (Figs. 2, 5). Hartman et al. [92] reported that the presence of ground-glass infiltrates on CT in the setting of AIDS allowed a











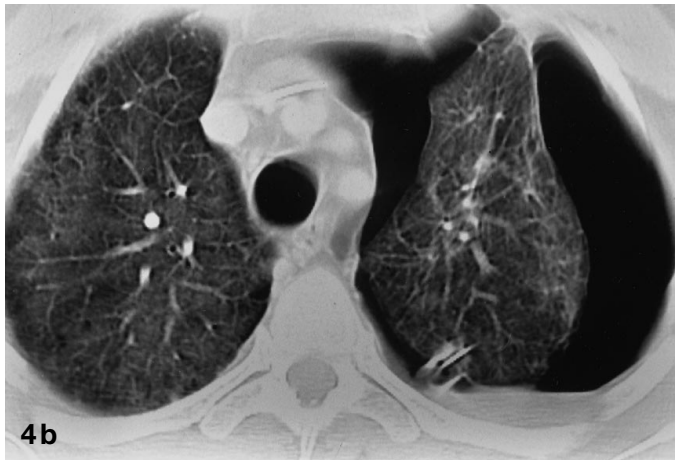
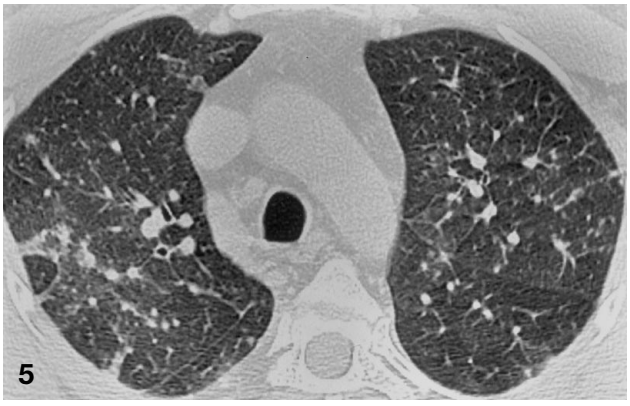


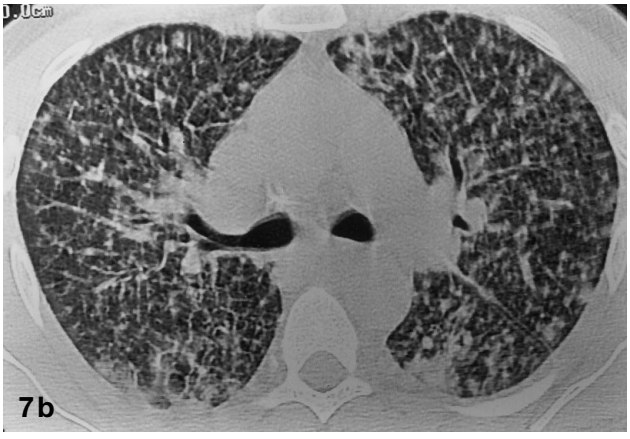
Fig. 1. A 70-year-old man presented with shortness of breath and 30-lb (13.6-kg) weight loss. Chest film shows 'soft,' bilateral ground-glass infiltrates in a classic pattern for *Pneumocystis carinii* pneumonia (PCP). The patient was subsequently found to be HIV-positive with a CD4 count of 2 cells/mm^3 and *Pneumocystis* organisms on bronchoscopy. [Reprinted with permission from Kuhlman JE, Juhl J (1998) Chest disease in the immunocompromised patient. In: Juhl P, Crummy A, Kuhlman JE (eds) Paul and Juhl's essentials of radiologic imaging, 7th edn. Lippincott-Raven Publishers, Philadelphia]

Fig. 2 a, b. Plain film and CT findings of PCP. A 27-year-old HIV-positive, homosexual man with increasing shortness of breath and PCP. **a** Chest film shows asymmetric involvement with ground-glass infiltrates affecting primarily the right lung. **b** CT scan of the same patient shows that the ground-glass infiltrates are really bilateral, being diffuse on the right and patchy in distribution on the left. [Part **a** reprinted with permission from Kuhlman JE, Juhl J (1998) Chest disease in the immunocompromised patient. In: Juhl P, Crummy A, Kuhlman JE (eds) Paul and Juhl's essentials of radiologic imaging, 7th edn. Lippincott-Raven Publishers, Philadelphia]

Fig. 3. Cystic, upper lobe PCP. A 32-year-old man with AIDS and CD4 count of 30 cells/mm^3. Coned-down view of the right lung apex shows cystic lung disease due to PCP

Fig. 4 a, b. A 43-year-old man with AIDS and PCP. The patient presented with spontaneous pneumothorax refractory to chest tube placement. CT demonstrates a large left pneumothorax, diffuse bilateral ground-glass infiltrates of PCP, and small peripheral cysts *(arrows)*. Rupture of subpleural cysts is believed to be the cause of spontaneous pneumothoraces in patients with PCP





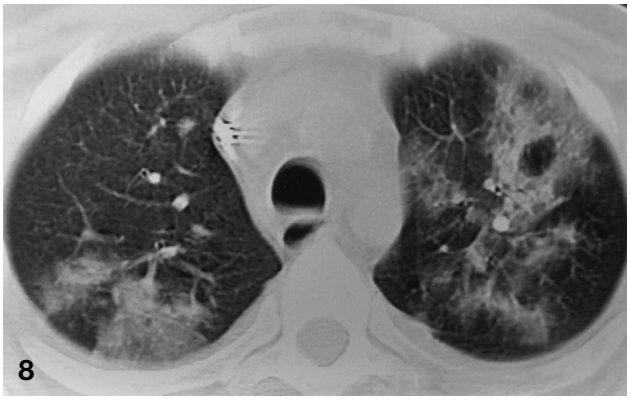


Fig. 7 a, b. A 27-year-old man with AIDS presented with increasing shortness of breath. **a** Chest film shows diffuse bilateral pulmonary infiltrates that are nonspecific. **b** High-resolution CT scan better characterizes the parenchymal lung disease and shows that it consists of a miliary pattern of small nodules with some thickening of the interlobular septa. This pattern is not typical for PCP, but more suggestive of disseminated mycobacterial or fungal infection. Cultures revealed disseminated *Histoplasmosis* infection

Fig. 8. Disseminated bacterial infection. A 34-year-old man with AIDS presents with acute onset of fever and sputum production. CT scan demonstrates patchy, bilateral areas of air space consolidation. Cultures grew *E. coli* from the lungs and blood

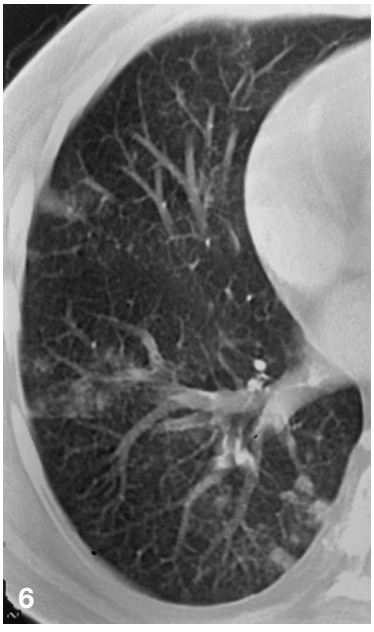
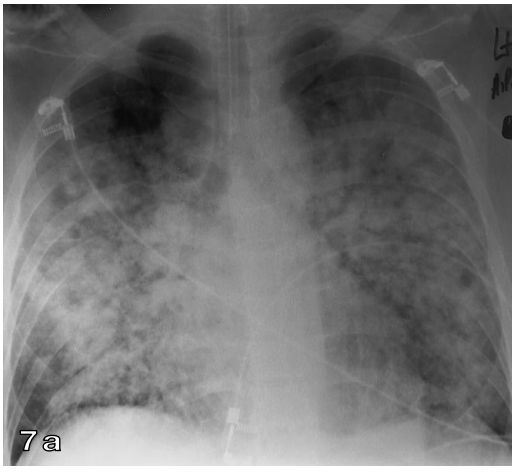


Fig. 5. CT findings of PCP. Patchy, bilateral ground-glass opacities due to PCP give a pattern of mosaic attenuation

Fig. 6. Unusual CT appearance of PCP in a 43-year-old man with AIDS and a CD4 count of 160 cells/mm^3. CT scan reveals scattered, poorly defined nodular opacities. Lung biopsy demonstrated granulomatous response to *Pneumocystis* infection



confident and correct diagnosis of PCP to be made in 94 % of cases. Interstitial and interlobular septal thickening may also be seen, often in the setting of chronic or recurrent PCP, and residual linear fibrosis, scars, and apical or subpleural air cysts may be identified in successfully treated patients long after the original infection has been cleared [17, 48, 89]. A less common presentation of PCP on CT is the presence of one or more pulmonary nodules (Fig. 6). These nodules when examined pathologically show a limited granulomatous response by the host to the infection.

A variety of nuclear scintigraphic agents have been employed to diagnoses PCP, the most widely used of which is gallium-67 citrate with a reported sensitivity of 80–90 % for PCP. Specificity of gallium scanning for PCP, however, is only 50–74 %, with other infections and AIDS-related lymphomas also accumulating gallium [93, 94 a]. Detection rates for PCP using gallium will depend on prior drug treatments and prophylaxis that alters the distribution patterns of the infection. A relative disadvantage of gallium scanning for the rapid diagnosis of PCP is that it often requires 24 and 48 h imaging [26]. Indium-111 labeled human polyclonal immunoglobulins will be taken up by lungs infected with *Pneumocystis,* but such uptake is not specific for PCP [28]. Radiolabeled monoclonal antibodies specific for *Pneumocystis* demonstrate high sensitivity (86 %) and specificity of (87 %) for the infection, but these agents

are only available at a limited number of investigational sites [93].

As the number of hospital admissions and deaths due to PCP has declined, other AIDS-related infections such as recurrent bacterial pneumonias, tuberculosis and fungal infections have increased in relative frequency and importance [5, 18].

Tuberculosis and other mycobaterial infections

Primarily because of AIDS, tuberculosis has re-emerged a serious worldwide health problem. Equally disturbing has been the emergence of multiple drug-resistant strains of tuberculosis that have appeared in Florida and New York City [2, 11, 94b–96]. TB cases in AIDS may be due to reactivation or primary infection, and because tuberculosis is a more virulent pathogen, this infection may present earlier than other opportunistic infections. The median CD4 count in HIV patients co-infected with TB is around 350 cells/mm^3, compared with < 200 cells/mm^3 in patients with PCP [1, 94b, 95].

The radiographic and CT features of tuberculosis in AIDS will depend on the severity of the immunosuppression [11, 97]. In early HIV disease, tuberculosis demonstrates classic findings of upper lobe infiltrates, cavities, and endobronchial spread. Skin tests are positive and the infection is confined to the lungs [1, 19]. As the degree of immunosuppression becomes more severe, tuberculosis manifests in patterns more reminiscent of primary infection, progressive primary disease, or disseminated and miliary disease. Such patients are usually anergic, with only 20–40 % able to produce a positive skin test for TB. The chest radiograph and CT may demonstrate diffuse infiltrates, multiple pulmonary nodules or miliary lesions, and prominent mediastinal adenopathy. The chest film may also be normal without evidence of lung lesions, even though the patient has disseminated TB [1, 2, 11, 19, 95].

Patients co-infected with HIV and TB are more likely to have adenopathy, pleural effusions, disseminated extrapulmonary TB, and miliary disease compared with HIV-negative patients with TB [11, 97]. Typically on CT, enlarged lymph nodes due to TB or other mycobacterial infections demonstrate rim enhancement with intravenous contrast administration [98, 99].

AIDS patients being treated for tuberculosis who are started on antiretroviral agents may demonstrate initial worsening of clinical and radiographic manifestations of their TB [20]. Radiographic worsening of TB correlates with the rise in the CD4 count and fall in the HIV viral titers in these patients [20].

Of the other mycobacterial infections seen in AIDS, *Mycobacterium avium* complex (MAC), formerly *Mycobacterium avium intracellulare* (MAI), is the most common [19]. This pathogen is usually encountered in patients with endstage AIDS and CD4 counts below 50 cells/mm^3 [19, 100]. It is usually a disseminated infection found in sputum, blood, bone marrow and urine samples of infected AIDS patients, and constitutional symptoms rather than respiratory complaints predominate [1, 100, 101]. On radiographs and CT, evidence of disseminated disease may be seen in patients with MAC including adenopathy, hepatosplenomegaly and thickened bowel walls (see Fig. 9f). Pulmonary lesions are less common with MAC compared with TB infections, but may include infiltrates, nodules, and cavities [11, 102]. Even with multiple drug therapy, prognosis is poor [100, 102].

Fungal infections

Many types of fungal infections occur in AIDS patients, with most representing disseminated diseases that occur in later stages of AIDS when the CD4 counts drops below 150 cells/mm^3 [1, 13, 17, 19].

Candida is the most common fungus found in AIDS patients and causes oral thrush and esophagitis early and late. Lung lesions (nodules and cavities) are relatively rare, and usually indicate disseminated candidiasis [19]. Pulmonary fungal disease is more likely to be due to *Cryptococcus neoformans, Histoplasma capsulatum,* or *Coccidioides immitis.* Cryptococcal pneumonia is associated with infection of the central nervous system in 70–85 % of cases [11, 59, 103–106]. Radiographic findings may include nodules, reticulonodular infiltrates, and mediastinal adenopathy [11, 59, 103–106]. Histoplasmosis, coccidiomycosis, and blastomycosis are infections seen in AIDS patients from endemic areas for these fungi (Fig. 7) [1, 19]. Small nodules (in histoplasmosis: Fig. 7), larger masses (in blastomycosis), as well as cavities, alveolar, interstitial and reticulonodular infiltrates with or without adenopathy have all been reported [107–109]. A normal chest radiograph may be seen in up to 50 % of AIDS patients with disseminated fungal infection [11, 108].

One fungal infection that is uncommon in AIDS patients is invasive pulmonary aspergillosis, because neutrophil and granulocyte functions are relatively preserved in HIV disease. With increasing longevity of AIDS patients, however, and increasing use of multiple drug therapies that suppress granulocyte function, cases of *Aspergillus* infection are increasing in number. *Aspergillus* infections usually occur in later stages of AIDS in the presence of neutropenia, broad spectrum antibiotics, and corticosteroid use [19, 110–112].

Bacterial infections

Recurrent, community-acquired bacterial pneumonias may be the presenting feature of HIV disease and are estimated to occur in up to 30 % of AIDS patients [2, 10, 13, 19, 107, 113]. Most pneumonias are due to *Streptococcus pneumoniae* and *Hemophilus influenzae* [19]. Intravenous drug users are also more susceptible to recurrent staphylococcal pneumonia and Gram-negative pneumonias including recurrent *Pseudomonas* infections [1] (Fig. 8). HIV-positive patients who are intravenous drug users may present with septic emboli as well.

Other unusual bacterial pathogens found in AIDS patients include *Branhamella catarrhalis, Rhodococcus equi, Nocardia, Legionella* species, and *Mycoplasma pneumoniae* [1, 2, 114–118]. Presentation is similar to that in the immunocompetent host, with acute symptoms, fever and sputum production [1]. Radiographs and CT usually show focal lobar or multilobar pneumonia, but bacterial pneumonias in AIDS tend to be more aggressive with more rapid progression of disease, development of cavitation, lung necrosis, and empyema. Bacteremia is more common as well [11, 19].

Bacillary angiomatosis is an unusual bacterial infection encountered in AIDS patients that is caused by *Bartonella henselae* (formerly *Rochalimaea henselae*) [119–121]. Vascular skin nodules caused by this infection may mimic Kaposi sarcoma. Spread to the lymph nodes, liver (peliosis), spleen, central nervous system, skeleton (osteolytic lesions), and lungs may occur [119–121]. In the chest, endobronchial lesions, lung nodules, interstitial lung disease, mediastinal adenopathy, pleural disease and chest wall masses have all been reported [119–121]. Mass lesions may demonstrate marked contrast enhancement on CT [119]. Diagnosis is made by biopsy and identification of bacilli in the specimen [119, 121]. The infection responds to erythromycin.

Parasites

Parasites such as *Cryptosporidium, Strongyloides,* and *Toxoplasma* are additional unusual pathogens that can cause pulmonary disease in AIDS [122, 123].

Cytomegalovirus and other pulmonary viruses

Cytomegalovirus (CMV) is often found coexisting with PCP in the lungs of AIDS patients. CMV is frequently cultured from sputum, blood, and urine samples of end-stage AIDS patients. Whether CMV causes significant pulmonary disease in and of itself is debated, but those with suspected CMV pneumonitis may respond to appropriate anti-CMV therapy [19, 124, 125]. CMV also causes severe esophagitis, colitis, adrenalitis, chorioretinitis, and encephalitis in AIDS patients [11, 125, 126].

Herpes simplex in AIDS patients causes mucocutaneous skin ulcerations, localized visceral involvement, disseminated infection, tracheobronchitis, and pneumonitis lung [1]. Other viruses found in the lungs of HIV-positive patients include Epstein-Barr virus and respiratory syncytial virus [1, 11]. It is now known that particular types of herpes viruses are associated with and probably represent the responsible cofactors for Kaposi sarcoma and a variety of lymphoproliferative disorders in AIDS.

Nonspecific interstitial pneumonitis

Nonspecific interstitial pneumonitis is a diagnosis of exclusion when chest radiographs show diffuse bilateral interstitial infiltrates and an extensive diagnostic evaluation including lung biopsy fails to reveal a specific pathogen. Typical biopsy findings show infiltration of the lung interstitium by pleomorphic, mononuclear inflammatory cells and extensive alveolar damage [19, 127, 128].

AIDS-related neoplasms

There is an increased incidence of certain malignancies in AIDS. Kaposi sarcoma and non-Hodgkin lymphoma are both AIDS-defining cancers as is invasive cervical carcinoma [13, 129]. Other tumors such as Hodgkin lymphoma, testicular cancer, squamous cell cancer of the mouth and anus, lung cancer, and hepatoma have also been reported in association with AIDS, but whether there is an increased incidence of these tumors in AIDS has yet to be established [101, 129, 130]. There are also a number of lymphoproliferative disorders in AIDS that may have chest manifestations, including AIDS-related lymphadenopathy syndromes (ARLS), lymphocytic interstitial pneumonitis (LIP), atypical lymphoproliferative disorder (ALD), and lymphomas of mucosal or bronchial associated lymphoid tissue (MALToma or BALToma) [131, 132].

Kaposi sarcoma. Kaposi sarcoma (KS) in AIDS may affect the lung, where it has a predilection for proliferating in the interstitium and in the peribronchial and perivascular lymphatics [19, 133–136]. AIDS-related Kaposi sarcoma is more aggressive than the classic form of Kaposi sarcoma seen in Eastern European males [137, 138]. It often involves the skin, mucous membranes, lymph nodes, gastrointestinal tract, lung, and visceral organs [131, 139]. In the United States, it occurs almost exclusively in seropositive homosexual or bisexual men and their sexual partners (~ 95 %) [2, 137, 138, 140–143]. The number of AIDS patients presenting with KS in the United States and other industrialized nations has decreased significantly in the last 5 years from 30–40 % to 15 % [6, 8, 133, 140, 144, 145]. Co-infection with human herpes virus 8 is believed to cause all forms of KS [131, 146].

KS is the most common neoplasm to affect the lung in AIDS [134, 136, 147–156]. Lung KS is usually seen when there is also involvement of other organs and the skin (77–95 % of cases) [17, 19, 133, 134, 136, 143, 147, 148, 151, 152, 154, 157–162], but reports of isolated lung KS have appeared in the literature [136, 148, 151, 157, 159, 163].

The diagnosis of pulmonary KS can be elusive, with only 30–40 % of patients with parenchymal involvement demonstrating typical violaceous endobronchial nodules on bronchoscopy [135, 141, 150, 153, 155, 160, 161]. Transbronchial biopsies are positive in only 10–20 % of cases and biopsies may be complicated by significant hemorrhage due to the vascular nature of the lesions [2, 19, 135, 150, 153, 155].

The chest radiograph and CT scan, however, are often very suggestive of KS [17, 134, 156] (Fig. 9). Pulmonary disease due to KS often demonstrates a definite predilection for the peri-bronchovascular spaces [17, 134,

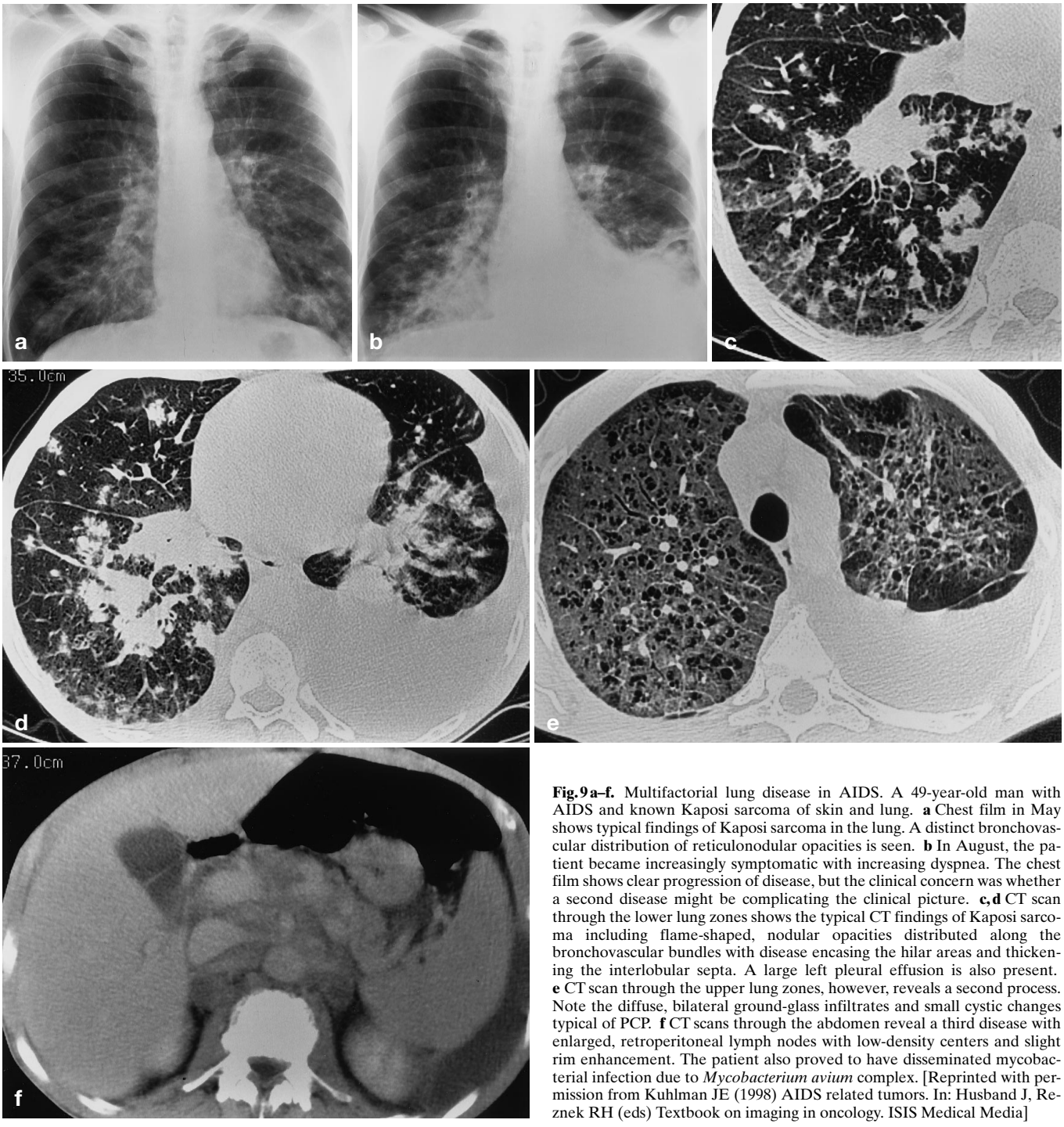


Fig. 9 a–f. Multifactorial lung disease in AIDS. A 49-year-old man with AIDS and known Kaposi sarcoma of skin and lung. **a** Chest film in May shows typical findings of Kaposi sarcoma in the lung. A distinct bronchovascular distribution of reticulonodular opacities is seen. **b** In August, the patient became increasingly symptomatic with increasing dyspnea. The chest film shows clear progression of disease, but the clinical concern was whether a second disease might be complicating the clinical picture. **c, d** CT scan through the lower lung zones shows the typical CT findings of Kaposi sarcoma including flame-shaped, nodular opacities distributed along the bronchovascular bundles with disease encasing the hilar areas and thickening the interlobular septa. A large left pleural effusion is also present. **e** CT scan through the upper lung zones, however, reveals a second process. Note the diffuse, bilateral ground-glass infiltrates and small cystic changes typical of PCP. **f** CT scans through the abdomen reveal a third disease with enlarged, retroperitoneal lymph nodes with low-density centers and slight rim enhancement. The patient also proved to have disseminated mycobacterial infection due to *Mycobacterium avium* complex. [Reprinted with permission from Kuhlman JE (1998) AIDS related tumors. In: Husband J, Reznek RH (eds) Textbook on imaging in oncology. ISIS Medical Media]

156, 164, 165]. Reticulonodular infiltrates are usually bilateral and more prominent in the perihilar and lower lung zones. On CT, a bronchovascular distribution of nodules and thickening of the interlobular septa are quite characteristic [17, 92, 134, 156, 165, 166] (Fig. 9). Less typical presentations include large masses, and vocal consolidation. These masses may show surrounding ground-glass density due to hemorrhage in the surrounding lung [92]. Pleural effusions may be seen when KS involves the pleural space and are often bloody [92, 134, 135, 154, 156]. Lymphadenopathy due to KS when present (30–35% of patients) is usually less extensive in the chest and mediastinum than elsewhere and may show enhancement with intravenous contrast [92, 151, 156, 159, 164, 167].

AIDS-related lymphoma. Between 2% and 5% of AIDS patients have an AIDS-related lymphoma and the numbers affected with this neoplasm are increasing [159, 168–179]. Lymphomas occur in AIDS when immunosuppression is severe; CD4 counts are usually below 50–100 cells/mm^3 [176, 179, 180]. Most are primarily

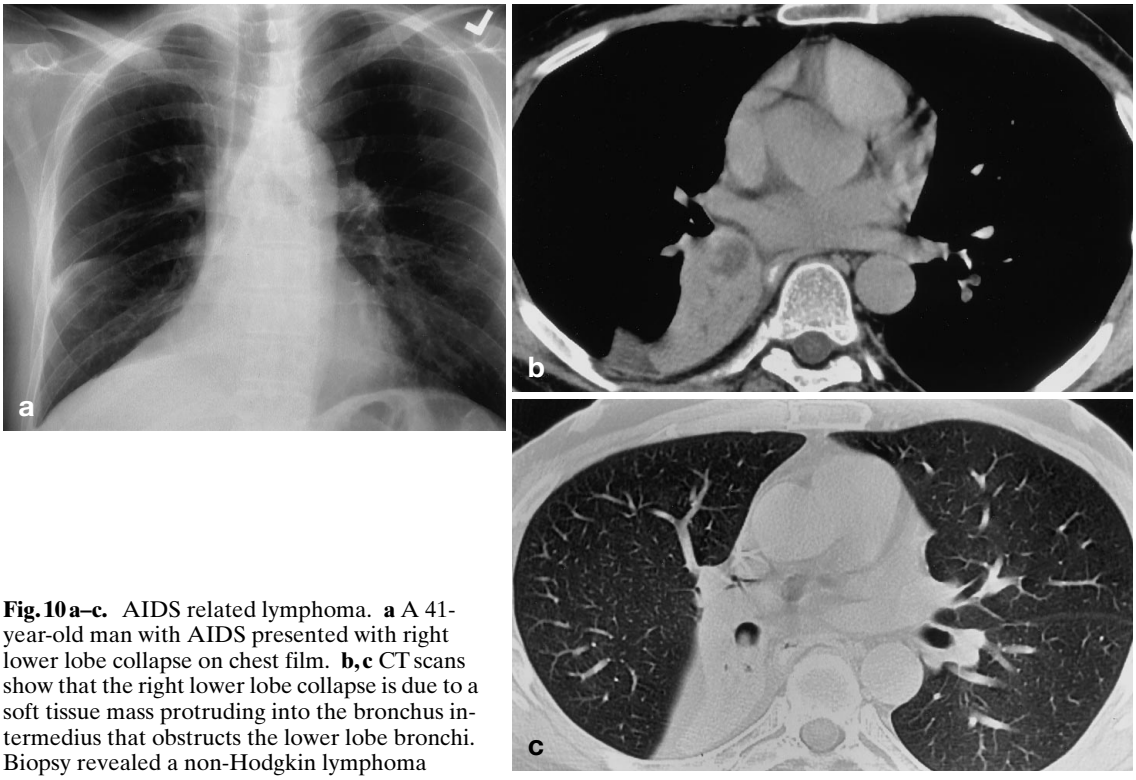


Fig. 10 a–c. AIDS related lymphoma. **a** A 41-year-old man with AIDS presented with right lower lobe collapse on chest film. **b, c** CT scans show that the right lower lobe collapse is due to a soft tissue mass protruding into the bronchus intermedius that obstructs the lower lobe bronchi. Biopsy revealed a non-Hodgkin lymphoma

non-Hodgkin B cell lymphomas, which are aggressive, high-grade tumors that include poorly differentiated large or anaplastic lymphomas, Burkitt's lymphoma, and immunoblastic sarcomas [170, 181, 182]. Herpes viruses are believed to be the responsible cofactors stimulating overproduction of B cells that results in lymphoma development [169, 183].

AIDS-related lymphomas often involve extranodal sites such as the bone marrow, bowel, liver, spleen, kidneys, central nervous system, and skin [1, 145, 169, 177, 180–182]. The chest may be involved in from 6% to 40% of cases, with lung involvement in 10–30%, hilar or mediastinal lymphadenopathy in 22–25%, and pleural effusions in 30–50% of patients [145, 159, 181, 183]. Chest wall masses, lytic bone lesions, and pulmonary nodules with or without lymphadenopathy have also been reported [10, 145, 181, 182]. Lung findings may include nodules, masses, reticulonodular infiltrates or airspace consolidation [183 a, 183 b] (Fig. 10).

Lymphoproliferative disorders in AIDS

Lymphadenopathy. Lymphadenopathy in AIDS may be due to infectious or neoplastic causes as well as lymphoid hyperplasia [184–187]. Lymphoid hyperplasia is seen in AIDS-related complex (ARC) and the persistent generalized lymphadenopathy syndrome (PGL) where adenopathy is present at two or more extra-inguinal sites for more than 3 months in the absence of other AIDS-defining illnesses, infection, or drug reaction [176, 184, 185, 188]. PGL may progress into an AIDS-related B cell lymphoma [172]. Extensive mediastinal adenopathy, however, is not part of the PGL syndrome and should suggest an alternative diagnosis such as mycobacterial or fungal infection, AIDS-related lymphoma, or rarely the lymphadenopathic form of Kaposi sarcoma [10, 15, 99, 131, 186, 187, 189].

Lymphoid interstitial pneumonitis (LIP). LIP when it occurs in a child less than 13 years of age is considered an AIDS-defining illness. It is also being recognized in adult AIDS patients [159, 190]. The chest film shows bilateral reticular or reticulonodular opacities with or without hilar and mediastinal lymphadenopathy [191, 192]. LIP usually occurs in HIV-positive children who are older than 1 year of age, while PCP, the major differential consideration, occurs between ages 3 and 6 months [192, 193]. Epstein-Barr virus has been implicated as the infectious cofactor in LIP [176].

MALTomas and BALTomas. A spectrum of lymphoproliferative syndromes in AIDS patients affect the lymphoid aggregates that are found in the submucosa of bronchi. Polyclonal hyperplasia of these lymphoid aggregates probably occurs as the result of immunosuppression and chronic antigenic stimulation [194]. Monoclonal proliferations of lymphocytes produces a lymphoma of the same tissues that has been termed a BALToma or MALToma [195]. Radiographic and CT findings of MALTomas include parenchymal peribronchovascular nodules, focal masses, or areas of lung consolidation [132].

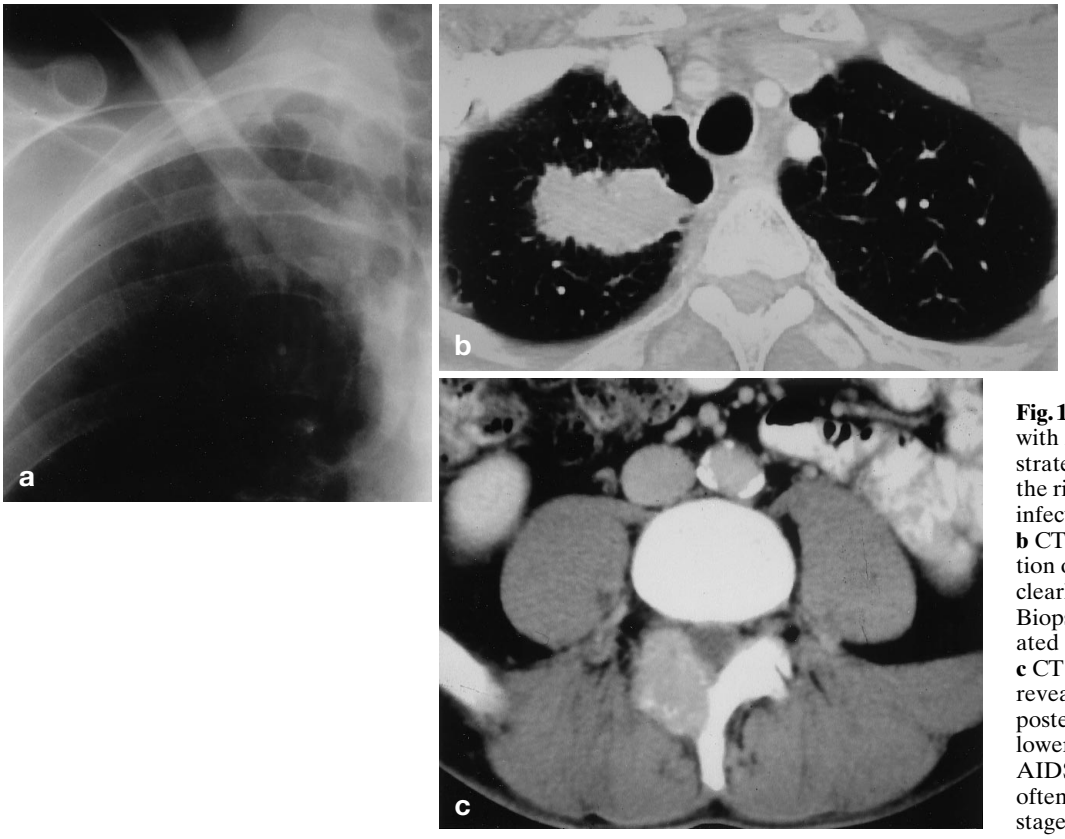


Fig. 11 a–c. A 38-year-old man with AIDS. **a** Chest film demonstrates a poorly defined opacity in the right lung apex, which could be infectious, or neoplastic in origin. **b** CT allows better characterization of the lung abnormality and clearly shows it to be a mass. Biopsy revealed an undifferentiated adenocarcinoma of the lung. **c** CT scan through the abdomen revealed a bone metastasis to the posterior elements of one of the lower lumbar vertebral bodies. AIDS patients with lung cancer often present with more advanced stages of disease

Lung cancer and other non-AIDS-defining malignancies

An AIDS patient with lung cancer is almost always a smoker and is more likely to be younger and have more advanced disease at presentation than a non-AIDS patients with lung cancer [141, 178, 187, 196–206] (Fig. 11). Whether there is an increased incidence of bronchogenic carcinoma in AIDS is not known; the data remains inconclusive to support or reject this hypothesis [18, 201–206]. Most lung cancers in AIDS patients, as in the general population, are adenocarcinomas [18, 201–206].

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