Pulmonary Infections in People Living with HIV

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KEYWORDS

• Thoracic imaging • Infection • Chest radiography • Computed tomography • People living with HIV

KEY POINTS

- Infection of the lungs and airways by bacterial, viral, fungal, and protozoal agents is common in people living with HIV (PLWH).
- Among PLWH, the combination of clinical and radiographic findings performs better than radiographic findings alone in the detection and follow-up of pneumonia.
- Despite the declining incidence of *Pneumocystis jiroveci* among patients with HIV, *P jiroveci* pneumonia (PJP) may be the presenting illness in PLWH.

INTRODUCTION

The landscape of HIV infection has forever changed since the introduction and massive implementation of combination antiretroviral therapy (cART) in 1996.[1] Before this date, natural history of HIV infection was dominated by a chain of opportunistic infections and cancers uncommon outside the HIV field, the so-called AIDS-defining conditions.[2] The relentless sequence of infections and cancer significantly impacted patients' quality of life, leading to patients' health deterioration and eventually death.[2] In fact, in 1981 the AIDS epidemic was heralded by the appearance of rare cases of pneumonia (*Pneumocystis jiroveci* pneumonia [PJP]) and uncommon skin cancer (Kaposi sarcoma), predominantly in men who had sex with men.[3]

The widespread adoption of cART, initially in high-resource countries, has changed the natural history of the disease, causing unprecedented declines in HIV-associated morbidity and mortality in people living with HIV (PLWH).[4] Immune reconstitution secondary to gaining control of viral replication led to sweeping decreases in AIDS-defining conditions.[5] However, it was noticed that PLWH had an excess of age-associated comorbidities, which soon became the most common cause of death in otherwise virologically controlled patients.[5] The success of cART caused an unparalleled increase in PLWH life expectancy with better quality of life and a shift in PLWH-associated comorbidities from infectious to noninfectious ones. Such a shift greatly diminished pulmonary infections, which had been a leading cause of morbidity and mortality in the pre-cART era.[6,7]

Since the introduction of cART, life expectancy of PLWH has substantially increased. The number of PLWH is increasing worldwide because of continued spread of disease and improved survival.[8] Three patient scenarios are relevant to pulmonary infections in PLWH.

1. PLWH having unrestricted access to medical care who adhere to modern cART and immunization schedules, and can achieve adequate immune reconstitution levels.
2. PLWH who have discontinued effective cART, who decline to seek medical care or adhere to cART, or who do not respond to cART.
3. PLWH who are unaware of their condition whose infection progresses to advanced stages of immunosuppression.

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Scenarios two and three are similar, both characterized by severe CD4 lymphopenia and the appearance of opportunistic infections reminiscent of those seen in the pre-cART era. In scenario one, the incidence of lung infection is superimposable to that of patients not infected by HIV; however, as the patient ages chronic lung disease can contribute to morbidity and mortality. Additional factors may modulate these scenarios including lung damage from host-dependent factors, such as exposure to toxins, smoking, and illicit or recreative drugs. Local ecology may influence the cause of infectious lung diseases, such as the prevalence of tuberculosis (TB) in the community. Finally, chemoprophylaxis or vaccination may modify the incidence of infectious lung disease in PLWH. These include *P jiroveci* primary and secondary prophylaxis, *Mycobacterium tuberculosis* chemoprophylaxis, pneumococcal, meningococcal, influenza, and (more recently) COVID-19 vaccines. All of them are included in the vaccination schedule for PLWH.[9]

Despite these advances, AIDS-related infections (particularly TB) and bacterial infections (particularly pneumonia and bacteremia) continue to be leading causes of hospital admission and in-hospital mortality in PLWH worldwide.[10] In this article, we review the epidemiologic, pathophysiologic, and imaging features of pulmonary infections in PLWH. Conventional chest radiography and chest computed tomography (CT) remain the most useful imaging modalities for evaluation of the immunocompromised patient presenting with a suspected pulmonary infection.

THE SPECTRUM OF INFECTIOUS LUNG DISEASES IN THE MODERN COMBINATION ANTIRETROVIRAL THERAPY ERA

Because of the reasons outlined previously the epidemiology of lung disease, particularly lung infections, has changed remarkably in PLWH over the last decades. Although the incidence of opportunistic infection has declined substantially, respiratory infection caused by opportunistic pathogens remains a significant cause of morbidity and mortality in PLWH.[11]

Currently, bacterial pneumonia ranks first among the causes of pulmonary infectious disease in PLWH, followed by PJP and TB. Endemic fungi, parasites, and viruses may contribute to the burden of infectious pulmonary disease worldwide; however, striking differences in the relative incidence of some pathogens depend on the geographic location.[12]

HIV infection is associated with a greater than 10-fold increase in the incidence of bacterial pneumonia.[13] Additional risk factors are intravenous drug use and smoking.[14] Although bacterial pneumonia can occur throughout the course of HIV infection, its incidence increases as CD4 cell counts decrease.[15] Recurrent bacterial pneumonia was included as an AIDS-defining condition by the Centers for Disease Control and Prevention in 1992. Controlling viral replication is protective against the development of bacterial pneumonia.[15] Data from randomized clinical trials have demonstrated that the risk of bacterial pneumonia is reduced by cART even when the CD4 count is greater than 500 cells/mm^3.[15]

IMAGING APPROACH

The evaluation of respiratory symptoms and suspected pneumonia in PLWH is challenging. Imaging plays a crucial role in the detection and management of PLWH with a suspected respiratory infection. Although some chest radiographic findings are pathognomonic for specific conditions, in most cases, the diagnostic process depends on correlating the chest radiographic findings with the clinical scenario. In some situations, the diagnosis may only be confirmed on follow-up radiologic study and clinical features.[16]

Focal airspace consolidation has been shown to be the most common manifestation of bacterial infection. However, chest radiograph has limited sensitivity for the detection of early infection, being normal in up to 10% of patients with proven pulmonary disease.[17–19] Serial chest roentgenograms can aid detection of pulmonary disease, but faint opacities may be difficult to detect. Furthermore, neutrophil counts are often low, and this may result in a poor inflammatory response, which may further decrease the sensitivity of the chest radiographs.[18]

Although CT is not recommended for the initial evaluation of PLWH with suspected pulmonary infection, it is especially useful in the assessment of patients with respiratory symptoms, a clinical suspicion for pneumonia or bacterial airway infections, and normal or nonspecific chest radiographs.[17,20] In addition, CT is an important adjunct to the physical examination, allowing evaluation for lymphadenopathy in regions that are not externally accessible (eg, mediastinum, intra-abdominal sites), and assessment of internal organs for evidence of infection.

The most common CT patterns in acute pulmonary infections are nodules, tree-in-bud appearance, ground-glass attenuation, consolidation, or a combination. Ground-glass attenuation is a common but nonspecific CT finding that may result from pyogenic, fungal, or viral pneumonia.[20,21] Proof of the cause of pneumonia is not obtained in most cases.

BACTERIAL INFECTIONS

Bacterial infections, including pyogenic airway disease and bacterial pneumonia, are the most common pulmonary infections diagnosed in PLWH. Like persons without HIV infection, the most common bacterial cause of community-acquired pneumonia among PLWH is *Streptococcus pneumoniae*. Other bacteria causing pneumonia include *Haemophilus influenzae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Less common pathogens include *Legionella*, *Rhodococcus*, and *Nocardia*.

Airway diseases caused by bacterial agents, such as *H influenzae*, *P aeruginosa*, *Streptococcus viridans*, and *S pneumoniae*, also occur with increased frequency in PLWH. These abnormalities are typically absent or subtle on chest radiographs. CT findings consist of bronchial dilatation and wall thickening, tree-in-bud appearance of centrilobular nodules, and branching opacities (**Fig. 1**). Recurrent bacterial bronchitis may lead to bronchiectasis.

Streptococcus pneumoniae

S pneumoniae is the most common causative agent of bacterial pneumonia in PLWH (40% of those for an etiologic diagnosis) and carries a high rate of bacteremia and recurrence.[22] Despite controversies, the introduction of pneumococcal conjugate vaccine together with the classical polysaccharide vaccine has led to recommended immunization schedule with pneumococcal conjugate vaccine 13/polysaccharide vaccine 23. The combination has been demonstrated immunogenic in PLWH; however, the durability of protection remains unknown.[15]

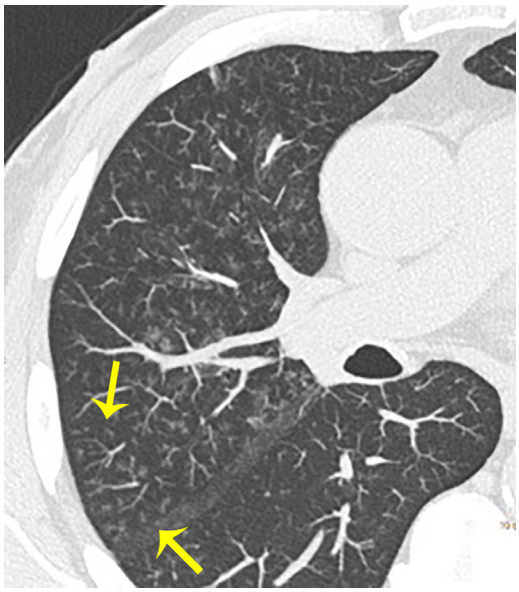

Fig. 1. Pyogenic airway disease. Thin maximum intensity projection reformatted CT image shows diffuse centrilobular branching nodular and linear opacities resulting in a tree-in-bud appearance (*arrows*).

The radiographic presentation of PLWH-associated bacterial pneumonia is like that in persons without HIV infection. Radiographically, acute pneumococcal pneumonia consist of a homogeneous consolidation that crosses segmental boundaries (nonsegmental) but involves only one lobe (lobar pneumonia) (**Fig. 2**). Because the consolidation begins in the peripheral airspaces of the lung, it almost invariably abuts against a visceral pleural surface, either interlobar or over the convexity of the lung.[11] Cavitation and pneumatocele formation are unusual, but when present suggest a polymicrobial infection. Pleural effusion is common and is seen in up to half of patients.

Occasionally, infection may manifest as a spherical focus of consolidation without visible air bronchograms that simulates a mass (round pneumonia) and is commonly located posteriorly and in the lower lobes (**Fig. 3**). Round pneumonia is a rare manifestation of lower respiratory tract infection in adults. It is primarily seen in children because they have poorly developed pathways of collateral ventilation and smaller alveoli. Although round pneumonias are usually caused by *S pneumoniae* or *H influenzae*, the work-up should also include evaluation for Q fever and *Legionella micdadei*.[23] In immunocompromised patients, round pneumonia may be the initial manifestation of a rapidly progressive, life-threatening lung infection.[24]

Haemophilus influenzae

H influenzae ranks second among the causes of bacterial pneumonia with etiologic diagnosis in PLWH.[25] It most often affects PLWH with advanced infection and with a subacute presentation.[25] Other factors that predispose to *Haemophilus* pneumonia include chronic obstructive lung disease (COPD), malignancy, and alcoholism. Pneumonia is often associated with a previous history of upper respiratory tract infection followed by onset of high fever, cough, dyspnea, purulent sputum, and pleuritic chest pain.[26]

The typical radiographic appearance of *H influenza* pneumonia consists of multilobar involvement with lobar or segmental consolidation and pleural effusion (**Figs. 4** and **5**). In 30% to 50% of patients, the pattern is that of lobar consolidation like that of *S pneumoniae*.[27,28]

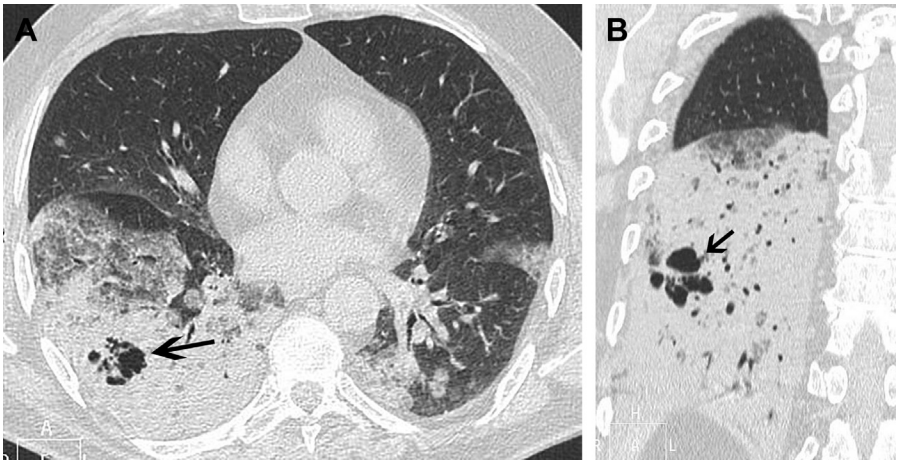

Fig. 2. Pneumococcal pneumonia. (*A*) Axial and (*B*) coronal CT images show heterogenous lobar consolidation with irregular air lucencies caused by necrosis (*arrows*).

Staphylococcus aureus

S aureus is the third most frequent cause of pneumonia in PLWH and is frequently community-acquired.[29] It is usually seen in intravenous drug users who develop tricuspid endocarditis with secondary pulmonary emboli.[30] PLWH have also been disproportionally affected by methicillin-resistant *S aureus* colonization even when on antiretroviral therapy.[31] Risk factors for the development of staphylococcal pneumonia in PLWH include underlying pulmonary disease (eg, COPD, carcinoma), chronic illnesses (eg, diabetes mellitus, renal failure), or viral infection.

The characteristic CT manifestation of *S aureus* is as a bronchopneumonia (lobular pneumonia) with or without cavitation or pneumatocele formation (**Fig. 6**). It is bilateral in approximately 40% of patients.[32] Pyogenic airway infections involving the walls of the bronchi and bronchioles result in airway wall thickening and dilation.[33] Pleural effusions occur in 30% to 50% of patients.

Pseudomonas aeruginosa

P aeruginosa was a common cause of bacterial pneumonia in the pre-cART era.[34] Difficult-to-treat chronic bronchopulmonary infections were described in PLWH with advanced

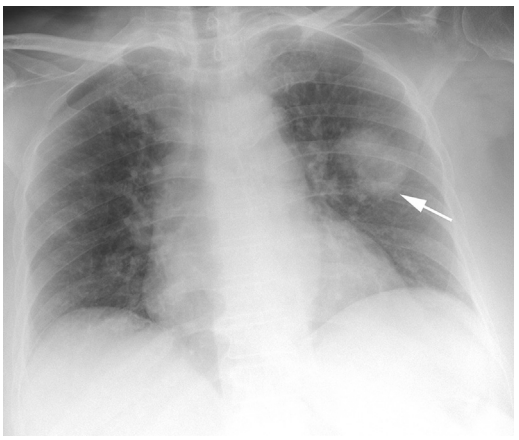

Fig. 3. Round pneumonia. Chest radiograph shows a masslike area of consolidation in the left upper lobe (*arrow*). Gram stains of sputum demonstrated *Streptococcus pneumoniae*.

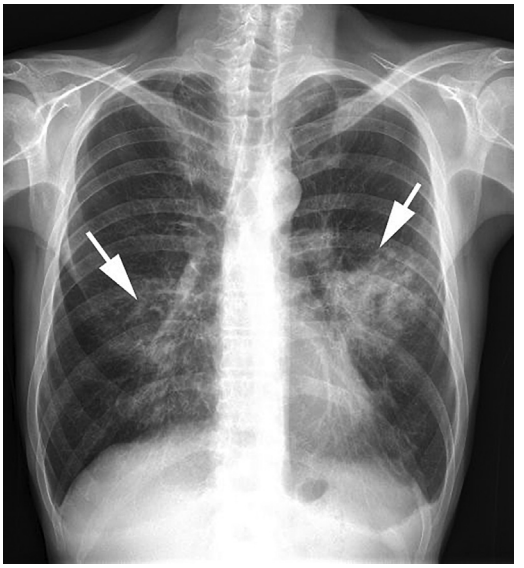

Fig. 4. *Haemophilus influenzae* pneumonia. (A) A 49-year-old man with fever. Posteroanterior chest radiograph shows bilateral areas of consolidation with ill-defined margins (*arrows*). A community-acquired *H influenzae* pneumonia was diagnosed.

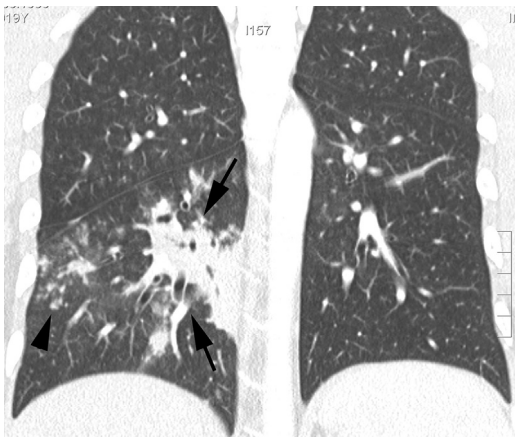

Fig. 5. Bronchopneumonia caused by *Haemophilus influenzae*. Coronal reformatted CT shows a focal area of consolidation in the right lower lobe with visible air bronchogram and poorly defined margins (*arrows*). Also evident are small nodular opacities and a few tree-in-bud opacities (*arrowhead*).

immunosuppression.[35] *P aeruginosa* causes confluent bronchopneumonia that is often extensive and frequently cavitates.

The radiologic manifestations are nonspecific and consist most commonly of patchy areas of consolidation and widespread poorly defined nodular opacities.[36] CT findings consist of multifocal, predominantly upper lobe, airspace consolidation, random large nodules, tree-in-bud opacities, ground-glass opacity, necrosis, and pleural effusion (**Fig. 7**).[37,38]

Other less common pathogens that can cause bacterial pneumonia in PLWH are *Legionella pneumophila*, *Rhodococcus equi*, and *Nocardia*, the two latter appearing in profoundly immunosuppressed patients.

Legionella sp

Legionella pneumonia is an infrequent cause of bacterial pneumonia in PLWH on antiretroviral therapy.[8] Other risk factors for *L pneumophila* pneumonia include posttransplantation, cigarette smoking, renal disease, and exposure to contaminated water.[39]

Imaging findings include consolidation that is initially peripheral, similar to *S pneumoniae* pneumonia. In many cases focal consolidation with a lower lobe predilection enlarges to occupy all or a large portion of a lobe (lobar pneumonia), to involve contiguous lobes, or to become bilateral.[40,41] Rapid progression of multilobar opacities with asymmetric distribution may occur despite an appropriate antibiotic therapy (**Fig. 8**). Occasionally legionella infections may result in a round pneumonia. Unilateral pleural effusions are common.[41]

Rhodococcus equi

R equi is a gram-positive, weak acid-fast coccobacilli that is isolated from the stools of foals. Rhodococcosis is a rare zoonotic infection that occurs in immunocompromised patients, such as transplant recipients and PLWH with a CD4 cell count less than 50 cells/μL. *R equi* pulmonary infection may mimic reactivated TB. Imaging manifestations consists of homogeneous nonsegmental airspace consolidation with or without cavitation, mediastinal or hilar lymphadenopathy, and/or multiple pulmonary nodules (**Fig. 9**).[42]

Nocardia

Nocardiosis is caused by members of the family Nocardiaceae, of which the most important genus is *Nocardia asteroides*. Nocardiosis is a rare cause of pulmonary infection in PLWH. The radiologic appearance of pulmonary nocardiosis is like that seen in immunocompetent patients. The most frequent imaging manifestations consists of homogeneous nonsegmental airspace consolidation that is usually peripheral, abuts the adjacent pleura, and is often extensive. Cavitation is common, seen in one-third or more of patients, and

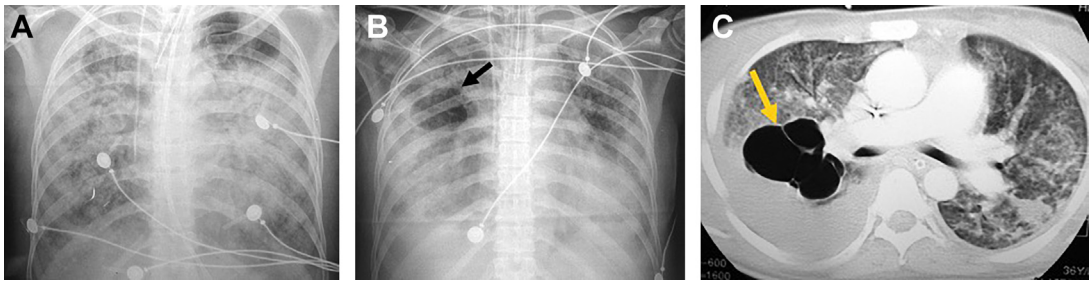

Fig. 6. Methicillin-resistant *Staphylococcus aureus*. (*A*) Portable chest radiograph shows extensive bilateral dense consolidations in upper lobes. (*B*) Follow-up radiograph shows a well-defined air-collection in the upper right lung (*arrow*). (*C*) CT shows a pneumatocele in the upper right lobe (*arrow*). A right pleural effusion is also demonstrated. Community-acquired methicillin-resistant *S aureus* pneumonia was diagnosed.

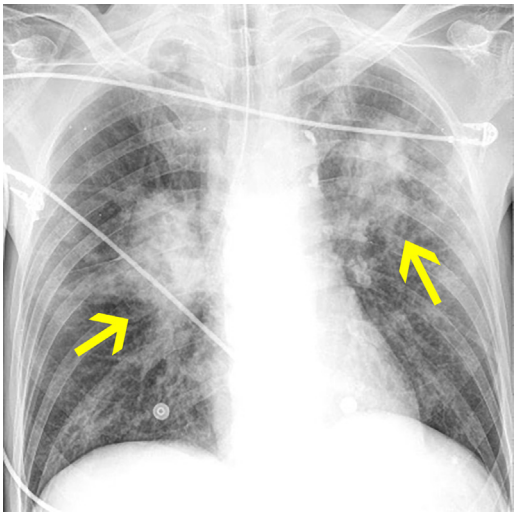

Fig. 7. *Pseudomonas* pneumonia. Portable chest radiograph shows extensive bilateral poorly defined areas of consolidation in the upper lobes (*arrows*).

may occur in areas of consolidation, within nodular opacities, or within masses (**Fig. 10**). Occasionally a halo of ground-glass opacity surrounds the nodule or mass.[43,44] Endobronchial spread can occur and infection can also extend directly to the pleura and chest wall, resulting in pleural effusion and chest wall abscess.[43]

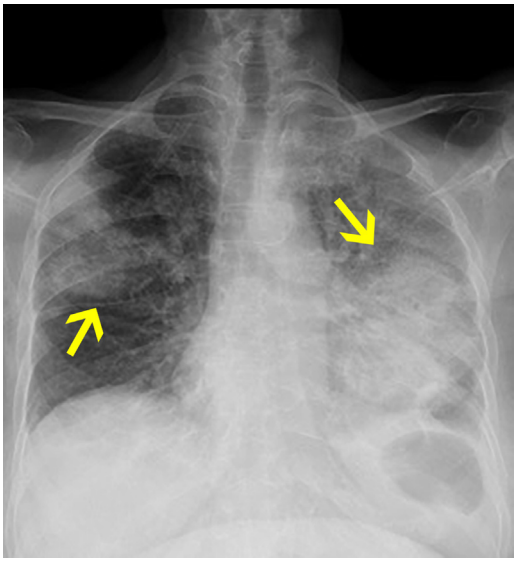

Fig. 8. *Legionella* pneumonia. Anteroposterior chest radiograph shows bilateral dense and poorly defined "rounded" consolidations in the right upper and left lower lobes (*arrows*). Community-acquired *Legionella pneumophila* pneumonia was diagnosed.

Mycobacterium tuberculosis and Nontuberculous Mycobacteria

Although cART reduces the incidence of opportunistic infections its initiation can also trigger a pathologic hyperinflammatory response to viable or dead *M tuberculosis*, known as TB immune reconstitution inflammatory syndrome.[45] Immune reconstitution inflammatory syndrome associated with TB is well recognized among HIV-infected patients initiating cART.

TB and nontuberculous mycobacteria (NTM) have killed more PLWH than any other group of infections. Although its incidence in HIV-infected patients has decreased with the use of antiretroviral therapy, at least one-third of patients infected with HIV worldwide are infected with *M tuberculosis*, and TB is the leading cause of death in PLWH residing in low-income and middle-income countries.[46] TB can occur at any stage of HIV-related disease but, with CD4 cell counts less than 200 cells/mm^3, disseminated infection occurs more frequently.[47]

Overall, the most common NTM resulting in pulmonary disease is the *Mycobacterium avium* complex (MAC).[48,49] NTM infections can appear as a classic form that mimics reactivation TB, in a bronchiectatic form, or as hypersensitivity pneumonitis.[50] Typical radiographic findings of MAC pulmonary infection include upper lobe involvement with or without cavitation (**Fig. 11**).[46,51] The cavities are usually thin-walled and frequently associated with apical pleural thickening. Endobronchial spread of disease is common and manifests as unilateral or bilateral small ill-defined nodules on chest radiograph. CT scan shows the nodules to be centrilobular and frequently

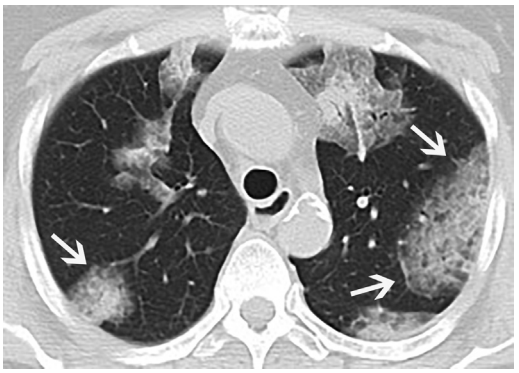

Fig. 9. *Rhodococcus equi* pneumonia. Axial CT shows large, rounded, ground-glass opacities in the periphery of both lungs (*arrows*). A geographic ground-glass pattern is observed in the anterior upper lobes. Patient presented with advanced AIDS and a CD4 cell count less than 100 cells/μL.

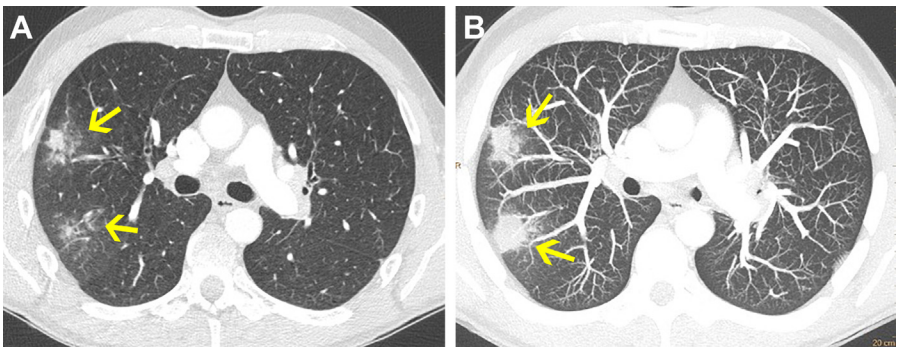

Fig. 10. Nocardial pneumonia. (*A*) CT at the level of the carina shows peripheral subpleural ill-defined nodules with surrounding ground-glass opacity (*arrows*). (*B*) On the thin maximum intensity projection reformatted image an associated halo sign is clearly demonstrated (*arrows*).

associated with branching opacities (tree-in-bud pattern) (Fig. 12).[52,53] Multifocal bronchiectasis is the most common radiographic feature of MAC in HIV populations.[48,49]

FUNGAL INFECTIONS

Fungal lung infections can occur in immune-competent and immune-compromised individuals. Their increasing incidence is likely multifactorial but caused in part by a growing population of immunocompromised individuals, including those living in resource-poor settings with a high incidence of HIV infections.

PLWH are at risk of developing fungal infections, which require intact T-cell function for containment. Fungal pneumonias other than PJP have been reported in PLWH, most commonly *Cryptococcus* and *Aspergillus*.[54–56] Other fungal infections are caused by *Histoplasma capsulatum* and *Coccidioides immitis*.[56] Incidence of invasive pulmonary aspergillosis (IPA) ranging from 3.5 to 19 cases of per 1000 person-years was observed in the 1990s but has substantially decreased with improvement in antiretroviral therapy.[57] Despite antiretroviral therapy, fungal opportunistic pneumonias are an important cause of mortality and morbidity among PLWH.[58]

Pneumocystis jiroveci

Pneumocystis is an opportunistic fungus associated with the AIDS-defining illness PJP. Formerly known as *Pneumocystis carinii*, the species infecting humans has been renamed *P jiroveci*.[54]

PJP was rare in the era before HIV/AIDS but its incidence increased dramatically during the early phases of the AIDS epidemic. PJP also develops in HIV-uninfected patients who are immunocompromised secondary to hematologic or malignant neoplasms, or caused by immunosuppressive therapy for stem cell or solid organ transplantation

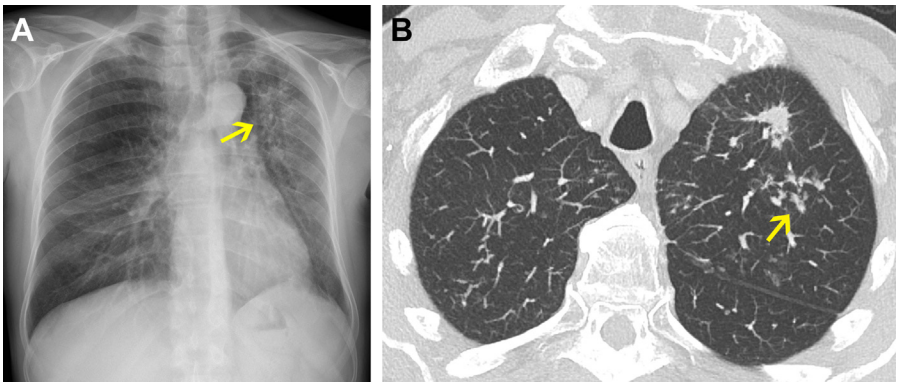

Fig. 11. *Mycobacterium avium*–intracellulare complex. (*A*) Posteroanterior chest radiograph shows an ill-defined left upper lobe opacity (*arrow*) with associated minimal collapse of the left upper lobe. (*B*) Axial CT image at the level of the left upper lobe shows a spiculated nodular opacity. Note the presence of a few tree-in-bud opacities nearby the nodule (*arrow*) representing NTM infection. The differential diagnosis and clinical concern were of a primary lung carcinoma.

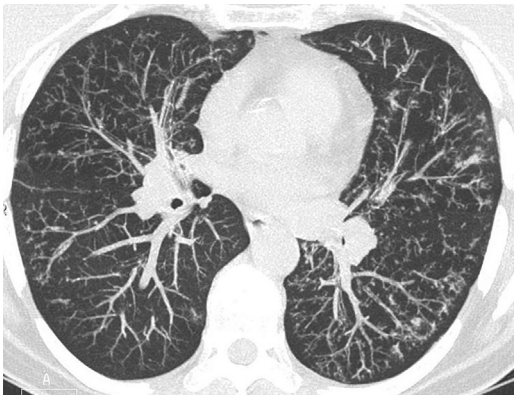

Fig. 12. *Mycobacterium avium*–intracellulare bronchiolitis. CT shows diffuse tree-in-bud opacities by NTM infection.

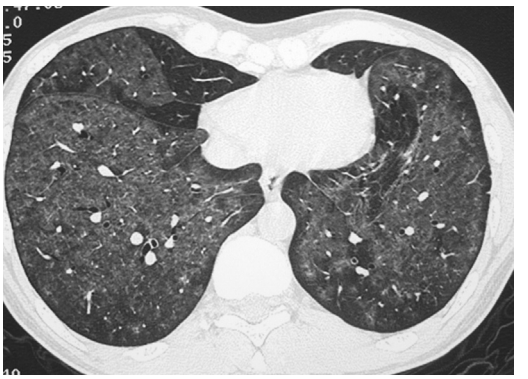

Fig. 13. *Pneumocystis jiroveci* pneumonia. CT shows extensive bilateral and homogeneous ground-glass opacities. Bronchoalveolar lavage showed *P jiroveci*.

or for autoimmune disorders.[55] *Pneumocystis* organisms can colonize the airways of children and adults with acute or chronic syndromes, such as COPD.[14,54]

The widespread implementation of cART and primary and secondary prophylaxis since 1987 dramatically reduced its incidence.[56] Currently, PLWH who fit in scenarios two and three are the most frequently affected, usually when the CD4 count falls to less than 200 cells/mm^3.[59]

Abnormal chest radiographs have been reported in up to 90% of patients with suspected PJP. Imaging findings consist of bilateral perihilar or diffuse symmetric interstitial pattern, which may be finely granular, reticular, or ground-glass in appearance (**Fig. 13**). As the disease progresses, alveolar infiltrates may also develop.

The widespread use of *P jiroveci* prophylaxis has led to a larger proportion of patients presenting with normal radiographs, such that a normal radiograph does not exclude the diagnosis. The most common CT manifestation of PJP consists of patchy or confluent, symmetric, bilateral ground-glass opacities. Less common manifestations include bilateral areas of consolidation, interlobular septal thickening, intralobular linear opacities, cystic lesions, and nodules.[60]

Cryptococcal Disease

Because most symptomatic cryptococcal disease is associated with CD4 counts less than 100/mm^3 its incidence has declined in the cART era. It remains a significant cause of opportunistic infection in PLWH in sub-Saharan Africa and in low- and middle-income countries.[61] The lung is the portal of entry, and cryptococcal pneumonia may present concomitantly or in the absence of cryptococcal meningoencephalitis, which is the most frequent and serious manifestation of cryptococcal infection.[62] HIV-negative patients have atypical presentations and worse outcomes with cryptococcal infection compared with PLWH.[63]

Radiographic features in pulmonary infection are varied and may reveal single or multiple nodular lesions (with or without cavitation), mass lesions, patchy airspace consolidations, interstitial infiltrates, mediastinal or hilar adenopathy, or pleural effusions (**Fig. 14**).[64–66] The most common CT findings consist of reticulonodular opacities, focal or widespread airspace consolidation, and ground-glass opacities.[64]

Invasive Pulmonary Aspergillosis

IPA is usually diagnosed in individuals with impaired immune function; those with neutropenia; solid organ transplant recipients; and patients on multiple drug therapies that suppress granulocyte function, such as high-dose corticosteroids.[11,67] In PLWH, major risk factors for IPA include CD4 cell counts less than 50 cells/mm^3 and neutropenia.[68]

Imaging findings are characterized by multiple, ill-defined, 1- to 3-cm-diameter nodules mainly involving the peripheral lung regions and the lower lobes.[69] Nodules may gradually coalesce into larger masses or areas of consolidation (**Fig. 15**). The classic radiologic finding associated with IPA is the halo sign, which is a rim of ground-glass opacity surrounding a pulmonary nodule.[70,71] The halo sign has also been observed in TB and mucormycosis. Cavitation in the nodules or masses occurs in 40% of affected patients and often results in an air-crescent sign.[34]

In addition, as with bacterial bronchopneumonia, imaging may also show segmental, lobar, or diffuse pulmonary consolidation; pleural-based densities; cavitary lesions; and/or less commonly pleural effusions.[69,71–73]

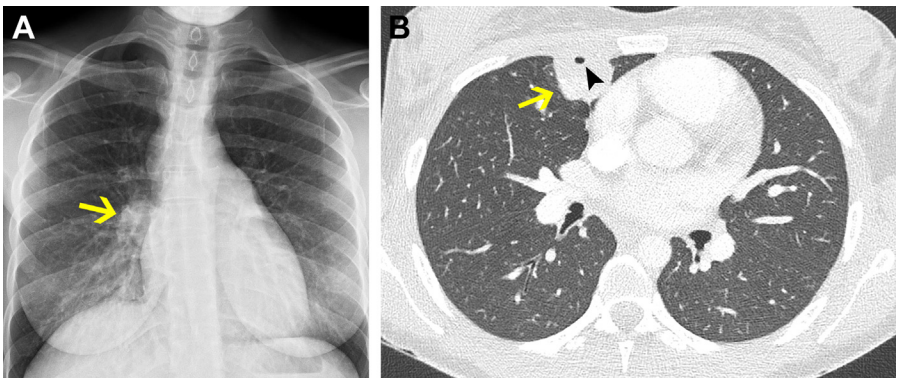

Fig. 14. Cryptococcosis. (*A*) Posteroanterior chest radiograph shows a nodular opacity adjacent to the right heart border (*arrow*). (*B*) Nonenhanced CT shows a cavitated mass in the middle lobe (*arrow*).

Endemic Fungi

Endemic fungi, such as *H capsulatum*, *C immitis*, and *Blastomyces dermatitidis*, may cause infection in PLWH in endemic areas (Southwest United States, northern Mexico, and parts of Central and South America). Latent infections can reactivate in individuals whose immune responses have been compromised, such as by corticosteroid therapy, immune-modulating agents, chemotherapy, or HIV.[74,75] Most cases of histoplasmosis or coccidioidomycosis are disseminated in PLWH with less than 100 CD4 cells/mm^3 (**Figs. 16** and **17**).[76] However, when the CD4 cell count is more than 250 cells/mm^3, focal pneumonia is most common.

Penicillium marneffei, a fungus endemic in Thailand and other countries in Southeast Asia, affects PLWH with greater than 100 cells/mm^3, causing disseminated disease with significant respiratory involvement.[77] Pulmonary disease can present with a wide range of imaging findings, including reticular opacities, consolidation, single or multiple nodules (including miliary nodules), lymphadenopathy, and pleural effusions.[50,78]

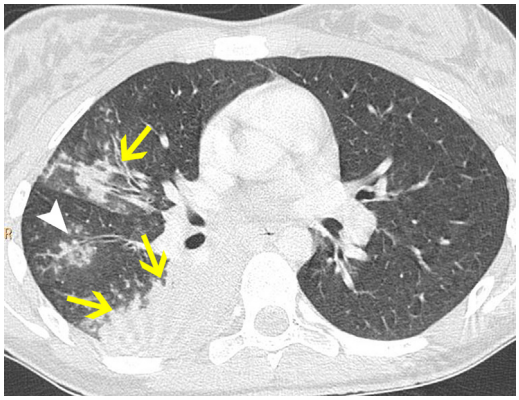

Fig. 15. Aspergillosis. CT image shows a homogeneous consolidation of the apical segment of the right lower lobe (*arrow*). Note the presence of a few tree-in-bud opacities nearby the consolidation (*arrowhead*). A focal consolidation is also visible in the middle lobe (*arrow*).

VIRAL INFECTIONS

Influenza is a common cause of respiratory illness in PLWH, although its incidence is reduced in the cART era.[28] During the influenza virus A/h1N1 pandemic, the prognosis of patients on well-controlled cART was similar to uninfected population.[29] International guidelines recommend annual influenza vaccination for PLWH.[8,22]

PLWH are particularly susceptible to pneumonias caused by cytomegalovirus (CMV) and herpesviruses. The presumptive role of CMV as a cause of pneumonia is uncertain until the CD4 cell count falls to less than 50 cells/mm^3. CMV pneumonia incidence in patients with AIDS has decreased dramatically since the introduction of cART.[79] CMV pneumonia, however, continues to be diagnosed in PLWH who fall into scenarios two and three in the introduction.

The CT scan manifestations of CMV pneumonia include multiple small nodular opacities, areas of consolidation, and ground-glass opacities.[80,81] The nodules tend to have a centrilobular distribution reflecting the presence of bronchiolitis. Small nodular opacities have also been reported in patients with adenovirus, influenza virus, herpes simplex virus, and herpes varicella-zoster virus pulmonary infections (**Fig. 18**).[82]

PARASITIC INFECTIONS

Toxoplasma gondii

Toxoplasma gondii is a well-recognized cause of parasitic opportunistic infection of central nervous system in patients with AIDS.[83] Pulmonary

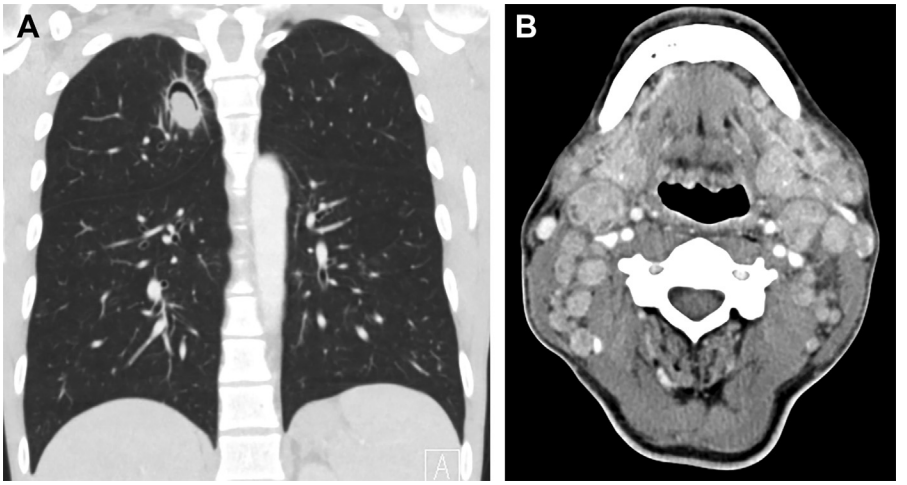

Fig. 16. A 34-year-old man living with HIV with disseminated coccidioidomycosis. (*A*) Necrotic cavity right upper lobe. (*B*) Extensive neck lymphadenopathy. Node biopsy positive for coccidioidomycosis.

toxoplasmosis is an infrequent manifestation of this infection. It can still be seen in the cART era but occurs mainly in patients with advanced immunodeficiency (CD4 cell counts <50 cells/mm^3).[84] The clinical and radiologic appearance of *T gondii* pneumonia are indistinguishable from those of PJP.[85]

COVID-19 IN PEOPLE LIVING WITH HIV

Several factors suggest that PLWH could be at increased risk of developing severe COVID-19.[86] Even on cART many PLWH have incomplete immune reconstitution and persistent immune activation. In addition, HIV infection is an independent risk factor for COPD, diffusing capacity impairment, asthma, and pulmonary hypertension. These noninfectious conditions, and the prevalence in PLWH of other risk factors for respiratory infections, such as smoking, are associated with increased COVID-19 severity.[86]

The prevalence of SARS-CoV-2 infection in PLWH ranges from 0.3% to 0.8%, similar to that in the general population. PLWH are reported to make up 0.8% to 2% of those patients hospitalized with COVID-19, which does not suggest increased hospitalization rates among PLWH.[86] Matched cohorts found no significant differences in adverse outcomes in PLWH hospitalized for COVID-19 compared with patients not infected with HIV.[87] A large prospective cohort in Spain, however, found greater age- and sex-standardized mortality from COVID-19 in PLWH than in the general population.[88] Recently, three population studies from the United Kingdom and South Africa concluded that living with HIV raises

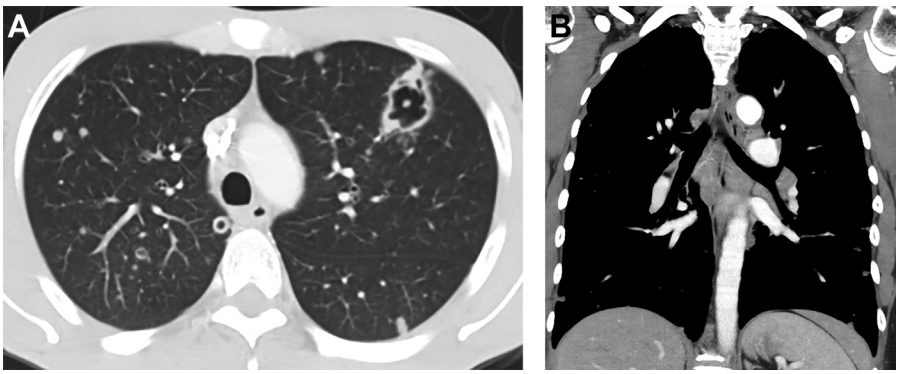

Fig. 17. Man living with HIV with disseminated histoplasmosis. (*A*) Dominant cavity left upper lobe with numerous other nodules, some cavitary. (*B*) Coronal mediastinal window demonstrates modest enlargement of mediastinal and hilar nodes.

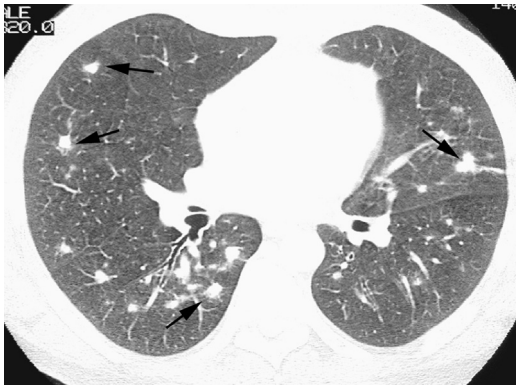

Fig. 18. Cytomegalovirus pneumonia. CT shows multiple scattered, poorly defined nodules (*arrows*) some of them surrounded by a halo of ground-glass opacity.

the risk of dying from COVID-19 (from 1.63- to 2.3-fold increased risk), after adjusting for age and other factors.[89,90]

SUMMARY

Although the wide availability of cART in high-income countries has shifted the burden of disease among PLWH toward chronic, age-related morbidities, infection remains a major cause of death and hospitalization worldwide. Infections with pyogenic bacteria, mycobacteria, and fungal pathogens remain more common than in the general population. Differential diagnosis in PLWH who have discontinued cART or were only recently aware of HIV infection and present with profound immunosuppression, differs considerably from PLWH successfully treated with cART. Although imaging manifestations of these infections are pleomorphic and may overlap with one another, knowledge of cART treatment status can help radiologists create a more tailored differential diagnosis and assist clinicians at the bedside.

CLINICS CARE POINTS

- Knowledge of antiretroviral therapy status is of paramount importance in assessing pulmonary infections in PLWH.
- AIDS-related and bacterial infections are the leading causes of pulmonary infection-related morbidity and mortality in PLWH.
- Streptococcus pneumoniae is the most common causative agent of microbiologically-proven bacterial pneumonia.
- Tuberculous and non-tuberculous pulmonary mycobacterial infections are a leading cause of morbidity and mortality in low- and medium-income countries.
- PJP is the most common AIDS-defining pulmonary infection in the era of modern antiretroviral therapy.
- HIV infection does not carry an excess risk of infection by SARS-CoV-2, but it carries a worse prognosis, especially in PLWH with uncontrolled HIV infection.
- Conventional chest radiography and computed tomography remain the most helpful imaging modalities for assessing suspected pulmonary infection in PLWH.

DISCLOSURE

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