Review of Radiologic Infectious and Non-infectious Pulmonary Complications in Human Immunodeficiency Virus Patients

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Abstract

The incidence of Human Immunodeficiency Virus (HIV) has decreased from its peak in the 1980’s yet there are currently more people living with HIV than ever before. As a result of highly active antiretroviral therapy (HAART), the number of opportunistic infections has decreased, with a concurrent increase in the number of non-infectious complications, not initially observed in the initial HIV epidemic.

The risk of developing HIV-related pulmonary complications is strongly influenced by the degree of immunosuppression, demographic characteristics, and the use of appropriate prophylaxis against HIV-associated opportunistic infections. This article reviews the radiographic and computed tomographic (CT) manifestations of common pulmonary infections and non-infectious pulmonary complications of HIV, and highlights the importance of clinical presentation, epidemiology and immunologic status.

Keywords: Human immunodeficiency virus; Pulmonary complications; Imaging

Introduction

Human Immunodeficiency Virus (HIV) was first reported in the United States in 1981; in 2012 there were more than 33.5 million people worldwide living with HIV/AIDS [1]. The introduction of highly active antiretroviral therapy (HAART) for the treatment of HIV infection has been accompanied by substantial reductions in mortality and incidence of opportunistic infections. As a result, there has been an increase in the number of non-infectious complications, not initially observed in the initial HIV epidemic; as patients are currently living longer with their HIV infection.

Pulmonary infections remain a leading cause of morbidity and mortality in patients with HIV infection worldwide. It is also one of the most frequent causes of hospitalization for patients infected with HIV worldwide [2]. About 70% of individuals infected with HIV will have at least one respiratory event during the duration of their disease [3]; therefore, it is almost certain that the pulmonary specialist will encounter the HIV infected patient.

This article reviews the radiographic and computed tomographic (CT) manifestations of common infectious and non-infectious pulmonary complications (Table 1) of HIV, and highlights the important relevant clinical features.

Infectious Pulmonary Complications

The risk of developing pulmonary infection with any given organism is strongly influenced by the degree of immunosuppression (CD4 T lymphocyte count, and HIV viral load), demographic characteristics, and the use of prophylaxis against common HIV-associated opportunistic infections (Table 2).

Bacterial pneumonia

Bacterial pneumonia is the most common infection in patients infected with HIV, and tends to occur earlier in the course of HIV compared to other opportunistic infections [4]. HIV patients have a 10-fold increased incidence of bacterial pneumonia compared with the general population in both industrialized and resource-poor countries [5]. Patients with a CD4 cell count of less than 200-250 cells/ul are at the highest risk for bacterial pneumonia [6,7]. The most common

Table 1: Infectious and non-infectious pulmonary complications in HIV patients.

| Type                        | Pathogen                          |
|-----------------------------|-----------------------------------|
| Bacterial pneumonia         | Pneumocystis jiroveci, Invasive Aspergillus, Cryptococcus |
| Fungal pneumonia            | Candida albicans, Coccidioides immitis, Histoplasma capsulatum |
| Mycobacterial pneumonia     | Mycobacterial tuberculosis, Non mycobacterial TB (MAC, M. Kansai) |
| Viral pneumonia             | Cytomegalovirus, Herpes Human Virus |
| Parasites                   | Toxoplasma, Strongyloides, Leishmania |
| Non-infectious Complications| Malignancies: Kaposi sarcoma, Non-Hodgkin B cell lymphoma, Adenocarcinoma of the lung |
| Interstitial lung disease   | Lymphocytic interstitial pneumonia, Non-specific interstitial pneumonia |
| Sarcoïdosis                 | |
| Obstructive lung disease    | Chronic obstructive pulmonary disease, Asthma, Bronchiectasis |

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Legionella is rare, the relative risk is about 42 times higher as compared to the general population [5].

Pneumococcal pneumonia is associated with bacteremia in up to 70% of patients [5]. This bacteremia is seen even in low-risk patients as defined by the pneumonia severity index. Lobar pneumonia, which is typically caused by Streptococcus pneumoniae, can also be associated with Klebsiella pneumoniae. Chest radiographs (CXR) usually shows classical air-space pneumonia: consolidation pattern towards the pleural surface with air bronchograms. There is usually minimal volume loss; in fact there may be increased volume of a lobe, seen as a bulging fissure. Occasionally, pneumonia can present as a focal nodule or mass, and cavitation and abscess are uncommon. Pleural effusion or empyema is present in less than 50% of patients. CT scan of the chest shows ground glass opacities and consolidation in lobar distribution (Figure 1). You may also see poorly defined centrilobular nodules (3-10 mm). Multiple smaller nodules should raise the possibility of viral pneumonia or mycoplasma infection (Figure 2).

Haemophilus influenzae pneumonia usually has a lobular pattern (i.e. multifocal bilateral patchy consolidations characterized by thick secretions within the bronchi) with predominance in the lower lobes. Tree in bud and centrilobular nodules may be observed on CT. Pleural effusions and cavities are rare.

Lung infections caused by Staphylococcus aureus can also produce lobular pattern. Volume loss is common and air bronchograms can be seen. Abscess and cavitations are frequent, producing a crescent sign on chest radiograph or CT. Other bacterial organisms associated with cavitations are Klebsiella, Streptococcus pneumoniae, or anaerobic bacteria. Pleural effusion occurs in about 50% of Staphylococcus pneumonia patients. Septic embolization to the lungs may be present, and is characterized by poorly defined nodules located peripherally, with predominance in the lower lobes that tend to cavitate. Septic emboli are seen in intravenous drug-users and patients with persistent bacteremia.

Legionella pneumonia can present as lobular or lobar pneumonia, progressing to bilateral consolidation in the majority of patients, despite proper therapy. It classically produces cavitation in immunosuppressed patients. However, it can initially present with rounded nodules, often peripherally situated, which could be mistaken for infarcts. Pleural effusions are seen in up to 30-60% of patients with Legionella.

The pattern of P. aeruginosa infection is non-specific, and it is difficult to distinguish it from other causes of pneumonia based on imaging alone. Nocardia can cause parenchymal nodules which can cavitate [8], and can be associated with brain abscess. Rhodococcus pneumonia in HIV patients tends to present as opacities in CXR with preference for lower lobes that can progress to cavitation [9].

Fungal pneumonia

Invasive aspergillosis: Imunosuppressed patients with a CD4 cell count less than 50 cells/ul are at risk for invasive aspergillosis (Figure 3) [10]. Typically chest CT will demonstrate multiple nodular opacities surrounded by ground-glass attenuation representing alveolar hemorrhage (halo-sign) (Figure 4). This sign is not specific for aspergillosis; and it can be found with other fungal infections (coccidioidomycosis, TB, nocardia, candida), viral infections (cytomegalovirus, herpes), pneumocystis pneumonia, granulomatosis with polyangitis (previously known as Wegener's granulomatosis), Kaposi sarcoma, and bronchoalveolar carcinoma. Advanced disease might lead to the progression of those nodules into cavities, the "air crescent sign", representing cavitation around central necrotic tissue (Figure 5).

Other well-known manifestations of Aspergillus pulmonary syndromes, such as aspergillomas, allergic bronchopulmonary aspergillosis, and chronic necrotizing pulmonary aspergillosis, are rarely reported with immunocompromised patients [11].

Pneumocystis pneumonia (PCP): Despite the widespread introduction of effective primary and secondary prophylaxis, P. jiroveci remains a common respiratory pathogen in individuals with AIDS. PCP usually develops in HIV-infected patients when the CD4 cell count decreases to <200 cells/ul and particularly to fewer than 100 cells/ul [12].

The chest radiography in a patient with PCP will typically show diffuse symmetrical opacities. Less frequently, there is perihilar “bat-wing” consolidation that might mimic pulmonary edema. If untreated, it may progress to air-space consolidation pattern. Normal chest radiographs and pneumatoceles with predominance in the upper lobes are found in up to 40 and 34% respectively [13].

The chest CT will commonly show a diffuse patchy ground-glass attenuation representing a intra-alveolar exudative process, leading subsequently to a consolidation pattern. Pneumatoceles, with variable size, shape and wall thickness, are more commonly observed (40%) when compared to CXR, and can lead to pneumothoraces (Figure 6). Small cysts are usually seen with upper lobe predominance, although they can be seen in any part of the lung and can resolve after treatment and clearing of the infection [14]. Mediastinal lymph node calcification is rarely found, being more common with tuberculous infections, histoplasmosis and sarcoidosis. Ground glass opacities are the most common dominant pattern seen on chest CT in HIV patients infected with PCP [8,15]. A ground glass pattern, can also be seen with CMV pneumonia, but is usually with a CD4 count less than 50 cells/ul [16].

Patients with HIV and PCP will have a greater extent of ground-glass opacities, rapid development of lung consolidation, and greater incidence of pneumatoceles than patients without HIV infection with PCP. Atypical features of PCP (less than 5%) include pleural effusions, hilar adenopathy, nodules, cavitary disease and miliary pattern.

Cryptococcosis: The second most common organ associated with cryptococcus infection after meningoencephalitis is the lung. Isolated pulmonary disease without dissemination can be seen in patients with

| Complications                        | CD4 (cells/ul) |
|--------------------------------------|----------------|
| **Infectious**                       |                |
| Bacterial pneumonia                  | <200-250       |
| Invasive aspergillosis               | <50            |
| Pneumocystis pneumonia               | <200           |
| Cytomegalovirus                      | <50            |
| Toxoplasma                           | <100           |
| Mycobacterium tuberculosis           | <200           |
| Non-mycobacterial tuberculosis       | <50            |
| **Non-Infectious**                   |                |
| Kaposi sarcoma                       | <200           |
| Lung cancer                          | >500           |
| Non-specific interstitial pneumonia  | <200           |
| Sarcoiosis                           | >200           |

Table 2: Correlation between pulmonary complications in HIV patients and CD4 count values.
higher CD4 counts. Chest radiography pattern mimics the presentation of PCP, usually showing a diffuse reticular pattern. Pleural effusion and hilar adenopathy are rare. CT chest may show a single or multiple nodules with or without cavitation; miliary pattern has also been described.

Other fungal infections: Lung lesions secondary to candida (nodules and cavities) are rare, and usually indicate disseminated candidiasis [17]. Histoplasmosis, coccidiomycosis, and blastomycosis are infections seen in AIDS patients from endemic areas for these fungi [17]. Pulmonary histoplasmosis might show small nodules, unilateral or bilateral lymphadenopathy (also found in coccidiomycosis) or calcified lymph nodes. Primary coccidiomycosis pulmonary infections usually will present as an air-space consolidation in the lower lobes with concurrent lymphadenopathy, and as the infection is treated it may resolve in some areas and recur in others. These consolidations may also progress to cavitations with thin walls. The presence of miliary pattern on CT chest or CXR should raise concern for disseminated coccidiomycosis, involving also bones, brain and skin. Blastomycosis dermatitidis may present as a large mass. A normal chest radiograph may be seen in up to 50% of AIDS patients with disseminated fungal infection [18].

Viral pneumonias

Cytomegalovirus (CMV): CMV is the most common viral infection
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Figure 3: Aspergillosis. Chest CT demonstrates bilateral peripheral irregular nodules with cavitation consistent with septic emboli to the lungs.

Figure 4: Aspergillosis with halo sign. Nodule surrounded by ground-glass attenuation representing hemorrhage referred to as the CT “halo-sign”.

Figure 5: Aspergillosis with air-crescent sign. Cavitation in advanced disease with “air-crescent” sign (arrow).

Figure 6: Pneumocystis pneumonia. Pneumatoceles, with variable size, shape and wall thickness, can lead to pneumothoraces in patients with PCP.

Parasitic pneumonias
Toxoplasma is seen in AIDS patients with encephalitis with a CD4 less than 100 cells/ul; however many cases of isolated toxoplasma pneumonitis have been reported. Toxoplasma gondii pneumonias are more common compared with infections secondary to mycobacterium-avium complex (MAC), CMV, and Herpes simplex virus (HSV) [20].

Findings on chest radiography are not specific: diffuse bilateral reticulonodular opacities can be seen, usually without significant mediastinal lymphadenopathy [21,22]. Chest CT will demonstrate the presence of patchy areas of ground-glass opacity, with some foci of consolidation.

Other parasites, including Strongyloides are unusual pathogens that can cause pulmonary disease in AIDS. It looks very similar to Strongyloides infection in non-immunocompromised patients with diffuse pattern on CXR and CT.

Mycobacterias
Mycobacterium tuberculosis (MTB): An estimated 70% of HIV patients with tuberculosis have CD4 counts < 200 cells/ul, especially in non-developing countries. This population is more likely to have lymphadenopathy, pleural effusions, disseminated extrapulmonary disease, and miliary disease compared with HIV-negative patients with MTB [18]. Overall, the radiographic characteristics will depend on the severity of the immunosuppression, and if the infection is primary or due to reactivation TB [23]. For example, if the patient has...
In primary tuberculosis infection, the chest radiograph will show a consolidation pattern with upper lobe predominance. If lobar consolidation is observed, it may be associated with lymphadenopathy [8], demonstrating central necrosis after intravenous contrast administration. Atelectasis can be present, and pleural effusions are commonly seen, but tend to be small and unilateral. Chest tomography with contrast will reveal adenopathy characterized by a necrotic center and peripheral enhancement (Figure 7).

Reactivation tuberculosis has a different pattern on CXR; the nodules with cavitation and consolidation are usually located with predominance in the apical segments of the upper lobes (85%) and superior segments of the lower lobes (15%) (Figure 8). Of note, cavitation is less common than in immunocompetent patients [25]. Miliary spread representing hematogenous dissemination from a pulmonary nidus and complex pleural effusion can be seen. Other differential diagnosis for military pattern includes MAC, toxoplasmosis.
and fungal infection [8]. On CT chest; the presence of centrilobular nodules associated with tree-in-bud opacities representing impact of small airway with pus suggests an active infection. Airway stenosis and tuberculoma can occasionally be found.

**Non mycobacterial Tuberculosis (NTM):** Patients with CD4 cell counts less than 50 cells/ul are at particular risk for NTM [24,26]. Mycobacterium Avium Complex (MAC) is the most common NTM infection seen in HIV patients [27], followed by *M. kansasii*. NTM is usually found as a concomitant infection with other pathogens [19].

MAC infections usually present as disseminated disease, in contrast to *M. kansasii* and *M. xenopi* which usually present as isolated pulmonary infection [20]. HIV patients who develop immune-reconstitution syndrome (IRIS) associated with MAC can present with homogeneous mediastinal and hilar lymphadenopathy on CT chest [28]. In immunocompetent patients, the most common radiographic finding is bronchiectasis [29], often involving the right middle lobe and lingula. The chest CT will usually show patchy consolidations representing foci of organizing pneumonia, small nodules usually centrilobular in distribution associated with air-space consolidation, and tree-in-bud opacities. Occasionally, solitary pulmonary nodules imitating malignancies can be found.

Other NTM species commonly present with bilateral reticular opacities [30]. In *M. kansasii* infection, consolidation and nodules tend to predominate in mid and lower lung zones, in contrast to immunocompetent patients. However, there are no specific radiographic findings to differentiate between the different NTM infections in HIV infected patients [30].

**Immune-reconstitution inflammatory syndrome (IRIS)**

IRIS is an inflammatory syndrome that represents immunological recovery of HIV patients after starting highly active antiretroviral therapy [31]. Diagnostic criteria include a) previous diagnosis of AIDS, b) increasing CD4 count and c) an exacerbation of opportunistic infections. Patients who develop IRIS usually have a prior CD4 less than 50 cells/ul with an excellent response to HAART. Symptoms usually present 2 to 8 weeks after starting HAART.

The infection most commonly associated with IRIS is MAC which is seen in up to 40% of HIV patients [32,33], and it is commonly associated with an endobronchial mass, lymphadenopathy or lymphadenitis [27], the latter producing upper airway compression [34]. Patients with mycobacterium tuberculosis who develop IRIS tend to have a prior diagnosis of TB, sharing with MAC lymphadenopathy with central low attenuation (73%) as a common feature. Although intra-abdominal nodes are most commonly seen (70%), axillary and mediastinal lymphadenopathy are frequent (40 and 36% respectively) [35]. Another common feature of mycobacterial infection associated to IRIS is the presence of bilateral pulmonary nodules (55%). Pleural effusions and endobronchial lesions are rare in MTB associated to IRIS.

**Non-Infectious Pulmonary Complications**

**Malignancies**

Kaposi sarcoma (KS): AIDS patients can have solitary pulmonary involvement up to 15% of the time when presenting with Kaposi’s sarcoma [19,36]. Those with a CD4 count less that 200 cell/ul are at high risk [37]. Kaposi's sarcoma may involve the airways, lung tissue, mediastinal lymph nodes and pleura. Since it presents with mucocutaneous lesions, the patient can present with airway obstruction or hemoptysis. On chest radiograph, bilateral symmetric ill-defined reticular or nodular opacities in a perihilar distribution are observed, along with pleural effusion and lymphadenopathy. CT chest will usually

![Figure 9: Kaposi sarcoma. CT of the Chest reveals irregular “flame-shaped” nodular opacities in a perihilar distribution with bronchovascular thickening.](image-url)
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reveal nodules with irregular margins (“flame-shaped”) [8] (Figure 9) in a peri-hilar distribution, pleural effusions (67%), lymphadenopathy (50%), and chest wall disease (53%) including ribs, sternum and thoracic spine [38].

Non-hodgkins lymphoma (NHL): Pulmonary involvement with non-Hodgkin's lymphoma rarely occurs (Figure 10). It typically occurs when the disease presents elsewhere in a generalized process simulating opportunistic infections. On CXR, isolated pleural effusions without parenchymal disease can be present in up to 70% of patients [19]. Also

Figure 10: Non Hodgkin lymphoma (NHL). CT chest reveals anterior mediastinal mass with areas of necrosis in a patient with NHL.

Figure 11: Lung cancer. Contrast-enhanced CT images of the chest demonstrates a large soft-tissue mass at the left hilar region with extension to the left upper lobe and lingula with encasement of the main pulmonary artery.
seen on CXR are sharply marginated nodules, lobar consolidations, diffuse interstitial patterns or masses. Of those, nodules are the most specific, although it is difficult to differentiate them from KS or opportunistic infection [39]. Importantly, in contrast to non-HIV patients with NHL, lymphadenopathy in the mediastinum is not prominent [19], being present only in up to 25% of cases [13].

**Lung cancer**

The incidence of lung cancer is increased in HIV patients regardless of their smoking history. Adenocarcinoma is the most common type of lung cancer seen [19]. Lung cancer in HIV patients tends to affect a younger population (mean age 46 years) [40] and is more aggressive. At the time of presentation, the usual CD4 count is usually above 500 cells/ul [37] and most of patients (75-90%) will have advanced disease upon diagnosis (stages III or IV), carrying a worse prognosis. Small studies [41,42] have shown that lung cancer in HIV patients tend to present as central/ peripheral mass or nodule (Figure 11), with upper lobe predominance, with extensive pleural disease at diagnosis and associated with concurrent infections (especially TB and PCP) [42].

**Interstitial lung diseases (ILD)**

Lymphocytic interstitial pneumonia and non-specific interstitial (NSIP) pneumonia are the most common types of ILD seen in patients with HIV disease. Their appearance on CXR and chest CT is similar to non-HIV-infected patients.

Non-specific interstitial pneumonia (NSIP): During the pre HAART era, the incidence of NSIP amongst HIV patients was approximately 38% [43,44]. The CD4 count tends to be lower than those patients with HIV and LIP (200 cells/ul) but can be in normal range as well [44]. Chest radiographs can be normal up to 50% of cases [45]. The usual abnormalities seen are a reticular, reticulonodular pattern or alveolar opacities. Pleural effusions and adenopathy are rare. NSIP does not have a pathognomonic appearance on HRCT but ground glass opacities that are predominantly at the bases, minimal honeycombing, along with areas of consolidation may suggest the diagnosis of NSIP.

Lymphocytic interstitial pneumonia (LIP): LIP is more frequently found in the HIV pediatric population. It is commonly seen in those with afro-Caribbean descent [44]. There are three main patterns that are commonly seen on chest radiography: a) reticulonodular opacities at bases, b) miliary pattern mimicking military TB but with larger nodules, c) dense alveolar opacities with combination of micronodules and reticular pattern [44]. HRCT usually shows reticular shadowing, fibrosis and honeycombing with areas of ground glass opacities and cystic lesions (Figure 12).

**Sarcoidosis**

HIV patients with sarcoidosis tend to have a CD4 count above 200 cells/ul. Typical stages of sarcoidosis in chest radiograph can be found, but these stages do not indicate disease chronicity nor do they correlate with changes in pulmonary function. In stage 1, there is predominance of bilateral hilar adenopathy; stage 2, mediastinal lymphadenopathy and reticulonodular appearance with less marked predominance of the upper lobes compared to non-HIV patients; stage 3 only reticulo-nodular pattern without lymphadenopathy and stage 4 usually represents fibrosis with small lung volumes, reticular opacification and traction bronchiectasis.

On HRCT, the presence of small nodules in a perilymphatic distribution with predominance of the upper and middle lobes along with mediastinal lymphadenopathy often with calcifications may suggest the diagnosis.

**Airway disease**

Patients with HIV have a higher incidence of asthma, chronic obstructive disease, and accelerated emphysema [46]. There is also an increase in bronchitis, bronchiolitis and the development of bronchiectasis regardless of smoking history. Those patients tend to have a CD4 count lower than 100 cells/ul [19]. Bronchitis, bronchiolitis and bronchiectasis usually will demonstrate absence of large airway disease on chest radiograph. CT chest is useful to demonstrate a tree-in-bud pattern, which is suggestive of bronchiolitis. When bronchiolitis is found bilaterally and with predominance in lower lobes, it is usually associated with bacterial infections [25]. When tree-in bud is found
distributed asymmetrically and associated with cavities or ring-enhanced lymphadenopathy, the possibility of mycobacterial disease should be considered [47]. Airway involvement by aspergillosis maybe unique in patients with HIV, presenting as obstructing bronchial aspergillosis, this is characterized by obstruction of bronchial wall, radiographically will present as bilateral and diffuse lower lobe consolidations [47].

**Pulmonary hypertension (PH)**

HIV infection is a known cause of type I pulmonary hypertension. It has also been associated with Human Herpes Virus 8 (also associated to KS) and can occur at any stage of HIV infection [19]. Clinical presentation is similar to those with idiopathic PH but is seen more often in younger patients [48]. The average CD4 count at time of diagnosis is 352 ± 304 cells/µl [49]. Chest imaging will not differ from non-HIV patients with pulmonary hypertension. The most common finding on CXR is cardiomegaly; and on CT chest it is enlargement of the diameter of the pulmonary artery [49]. The diameter of the main pulmonary artery can be easily measured on chest CT, values above 29 mm are suggestive of PH. Another method is to compare the diameters of the aorta and the main pulmonary artery. If the pulmonary artery diameter is greater than the aortic, then high pulmonary pressures are likely present. CT chest can reveal right atrial and ventricle enlargement, intraventricular septal bowing towards the left ventricle and a mosaic pattern suggesting areas of non-homogeneous perfusion.

**Conclusion**

The radiologic manifestations of pulmonary diseases in HIV patients are not specific and tissue sampling by bronchoscopic lavage or lung biopsy for microbiologic and histopathologic analysis may be needed to establish a diagnosis. However correlation of the radiologic findings with the immunologic staging, clinical presentation and epidemiology of the patient may offer valuable clues that can aid in the diagnostic process.

**Author Contributions**

JCG, AT, MN, PM, and RDS have participated in the manuscript writing. JCG is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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