Noninfectious Pulmonary Complications of Human Immunodeficiency Virus Infection

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Abstract: Human immunodeficiency virus type 1 (HIV-1) is the retrovirus responsible for the development of AIDS. Its profound impact on the immune system leaves the host vulnerable to a wide range of opportunistic infections not seen in individuals with a competent immune system. Pulmonary infections dominated the presentations in the early years of the epidemic, and infectious and noninfectious lung diseases remain the leading causes of morbidity and mortality in persons living with HIV despite the development of effective antiretroviral therapy. In addition to the long known immunosuppression and infection risks, it is becoming increasingly recognized that HIV promotes the risk of noninfectious pulmonary diseases through a number of different mechanisms, including direct tissue toxicity by HIV-related viral proteins and the secondary effects of coinfections. Diseases of the airways, lung parenchyma and the pulmonary vasculature, as well as pulmonary malignancies, are either more frequent in persons living with HIV or have atypical presentations. As the pulmonary infectious complications of HIV are generally well known and have been reviewed extensively, this review will focus on the breadth of noninfectious pulmonary diseases that occur in HIV-infected individuals as these may be more difficult to recognize by general medical physicians and subspecialists caring for this large and uniquely vulnerable population.


Chronic HIV infection preys on the immune system and renders individuals susceptible to a range of opportunistic infections not seen in the immunocompetent host. A diagnosis of HIV infection in the mid-1980s resulted in a rapidly fatal course in most individuals as there were no therapies available to limit viral replication. However, the advent of highly active antiretroviral therapy (HAART, now known simply as antiretroviral therapy or ART) almost 20 years ago transformed HIV into a chronic disease with a much more optimistic prognosis, and individuals who are adherent to ART are now living more than 3 decades with the disease. Unfortunately, it remains a “chronic disease” and not merely a silent infection, and persons living with HIV still suffer greater morbidities and mortality than the general population despite the incredible advances in the field. Due to the immunosuppressive nature of the disease, including its primary (albeit not exclusive) infection and ultimate depletion of CD4+ T-cell lymphocytes, clinicians naturally focus on infectious etiologies when these patients present to medical attention. However, while opportunistic infections still remain a significant concern in HIV-infected individuals, an impressive body of research spanning epidemiologic studies to cell culture models emphasizes the importance of noninfectious diseases in this population as well. HIV clearly affects the body in ways beyond T-cell biology alone. Pulmonary disorders remain a significant source of morbidity and mortality even in the current era, and the broadening scope of the manifestations of chronic HIV infection requires treating clinicians to expand their previous differential diagnoses for respiratory complaints even in the context of adherence to ART. New therapies for the disease have in fact brought with them a host of new complications previously not seen in HIV infection, such as sarcoidosis. In this article, we review the major noninfectious pulmonary complications of HIV infection and emphasize the current areas of interest from both a research and a clinical perspective.

Part 1: HIV-Associated Airway Diseases

Disease of the airways, particularly asthma, emphysema and bronchiectasis, have all been associated with HIV infection. Asthma, which is characterized by airway inflammation and reversible airflow limitation, can cause significant morbidity and even mortality. Epidemiologic data examining the relationship between HIV infection and asthma have been mixed, with some studies showing that HIV-infected patients have increased levels of airway hyperreactivity, a feature common in asthma and others failing to show an association. The Veterans Aging Cohort Study thus far suggests that HIV is not associated with higher rates of asthma, whereas other studies indicate a higher rate than expected.

In contrast, an association between emphysema and HIV infection seems clearer, with the first evidence of an association emerging more than 2 decades ago. Cohort data, again from the Veterans Aging Cohort Study, support this association and suggest that HIV infection confers a statistically significant increase in rates of chronic obstructive pulmonary disease (COPD; a clinical term encompassing emphysema and chronic bronchitis). Data from International Classification of Diseases-9 (ICD-9) codes entered during hospitalizations and patient self-reports support such an effect as do studies using spirometry to evaluate cohorts of HIV-infected individuals.

Bronchiectasis, which is characterized by pathologic dilation of conducting airways, impaired mucociliary clearance and recurrent infections, has been reported to be increased in the pediatric HIV population. Moreover, several studies have shown a higher-than-expected rate of bronchiectasis in persons living with HIV. The association is not surprising as recurrent and/or severe airway infections are risk factors for the development of bronchiectasis, and even otherwise healthy individuals living with HIV have much higher rates of acute bronchitis and bacterial pneumonia than the general population.
Pathogenesis

The etiology of airway disease in HIV-infected individuals is certainly multifactorial, but several specific mechanisms merit discussion. Cohort data suggest a possible association between the development of asthma and bacterial or *Pneumocystis jiroveci* pneumonia, as well as an elevated sputum eosinophil count in a significant number of affected individuals.\(^5\) In addition, certain chemokines, such as RANTES, have been implicated in both asthma and HIV infection.\(^14,15\) Tobacco use is almost certainly playing a role and it is well known to affect asthma control, and rates of tobacco use continue to be high among HIV-infected individuals.\(^16\)

In persons living with HIV who meet clinical criteria for COPD, tobacco use is clearly a major factor but this alone does not explain their increased risk when compared with uninfected individuals with similar smoking histories. Therefore, other mechanisms must be contributing to the pathogenesis of earlier and/or more severe airway destruction in these individuals. One cohort study examining the relationship between obstructive lung disease and HIV infection found a significant increase in viral load in those developing COPD\(^17\) even though CD4 counts were similar between the groups with and without COPD. Experimental models have identified that HIV-related viral proteins, which are present in relatively high concentrations in the airway, cause lung epithelial barrier dysfunction and impair innate immunity as reflected by a decreased ability to clear a bacterial challenge from the lung.\(^18,19\) Respiratory muscle function, which can be clinically relevant in the later stages of obstructive lung diseases, is also diminished in HIV infection.\(^20\) In addition, coinfections may play a role as studies in animal models show that *Pneumocystis* colonization may render the lung susceptible to the development of emphysema.\(^21,22\)

In addition, the overall inflammatory milieu within the airways in HIV-infected individuals may also play a role, with some studies showing that alveolar macrophages produce enzymes such as matrix metalloproteinases that degrade tissue in areas of emphysematous lung.\(^23\) In parallel, oxidative stress, which likely contributes to the development of COPD in general,\(^24\) is significantly increased in the airways of HIV-1 transgenic animals.\(^25,26\) These experimental findings are consistent with the long-recognized indices of oxidative stress and glutathione deficiency in persons living with HIV.\(^26\)

As would be expected, bronchiectasis seems to be associated with HIV infection in the setting of bacterial pneumonia and acute bronchitis. However, in at least 1 pediatric case series, lymphocytic interstitial pneumonitis, also known as lymphocytic interstitial pneumonia (LIP; which is much more common in HIV-infected individuals) was associated with the development of bronchiectasis even in the absence of chronic infections.\(^27\) In addition, analyses of sputum samples from HIV-infected children with bronchiectasis found high levels of interleukin-8 (IL-8) and immunoglobulin E (IgE) and positive cultures for either the bacteria *Haemophilus influenzae* or the virus parainfluenza in almost half of the subjects.\(^28\) Although at present one cannot state definitively that HIV-related infections are a direct cause of bronchiectasis, the prevailing view among experts is that bronchiectasis is increased in HIV-infected individuals as a result of more frequent and/or more severe airway infections that mediate airway wall damage.

Clinical Aspects

In terms of general pulmonary function, HIV-infected individuals studied in several cohorts have normal airflow at baseline\(^29,30\) but their diffusing capacity of carbon monoxide seems to be diminished.\(^31\) Whether the latter finding represents early emphysema or pulmonary vascular disease is unknown. In some cohorts, airflow limitation has been linked specifically to the use of antiretroviral medications.\(^32,33\) Consistent with these findings, abnormal declines in airflows as assessed by spirometry have been documented in both smokers and non-smokers on ART.\(^34\)

The presentations of airway diseases are not different in HIV-infected individuals and include the typical complaints of dyspnea on exertion, cough and wheezing. In this context, the clinician caring for these individuals should use the same diagnostic tests to distinguish asthma, COPD and bronchiectasis as would be used in individuals without HIV. Specifically, in addition to a thorough history with a particular emphasis on tobacco use, routine pulmonary function testing and chest imaging are usually sufficient to make an accurate diagnosis. As in the general population, HIV-infected individuals with asthma may have a normal lung examination during exacerbation-free periods, and diminished breath sounds and end-expiratory wheezing can occur in both asthma and emphysema depending on the severity of the disease. Chronic bronchitis, which is part of the COPD spectrum, and bronchiectasis are characterized by bothersome chronic coughing that is typically productive of significant amounts of sputum (particularly in bronchiectasis). More severe cases of bronchiectasis may present with constitutional symptoms (including low-grade fevers, night sweats and weight loss) that should prompt a search for atypical infections including those caused by *Mycobacterium avium* complex and fungi.

Tobacco cessation is an essential cornerstone of pulmonary management in the HIV-infected population due to the increased risk conferred by tobacco use in the development of airflow-limiting diseases.\(^35,36\) Specific data on the treatment of these diseases in the HIV-infected population are limited, but case reports suggest caution with the use of inhaled corticosteroids and the protease inhibitor ritonavir\(^37\) as this combination seems to confer a higher risk for steroid-related complications.

Part 2: HIV-Related Interstitial Lung Diseases

Certain interstitial lung diseases (ILD) have also been associated with HIV infection. More importantly, the differential diagnosis for ILD is altered and reordered by the presence of HIV and treatment with ART. In the pre-HAART era, a number of ILDs were described in HIV-infected patients that were thought to arise from systemic immune dysregulation, including nonspecific interstitial pneumonitis (NSIP) and LIP. In the current ART era and subsequent stabilization of underlying immune function, other ILDs are being recognized and described.

Pathogenesis

The various HIV-related ILDs have been tied to a number of experimental mechanisms, but no clear unifying etiology has emerged beyond the broad categories of immune dysregulation and reconstitution as well as some associated coinfections. LIP, which is seen in several rheumatologic disorders including Sjögren’s syndrome and rheumatoid arthritis,\(^38\) is characterized by an influx of lymphocytes into the alveolar space. It is thought to represent part of a spectrum of lymphoid pneumonidites that also includes NSIP and follicular bronchiolitis. An association between HLA-DR5 and HLA-DR6 in blacks and HLA-DR7 in whites has been found in HIV-infected individuals presenting with CD8+ lymphocytic infiltrates,\(^39\) termed diffuse infiltrative lymphocytosis syndrome. The pulmonary infiltration, in particular, is thought to be due to recruitment by chemoattractants, redistribution of
blood to the lungs and a proliferation of CD8+ T cells in situ in response to viral antigens with local elaboration of inflammatory cytokines. The presence of HIV and HIV-related proteins in germinal centers, the pulmonary interstitium and bronchoalveolar lavage fluid of patients with LIP support a direct causative role for the virus in this condition. In contrast, other evidence suggests a role for coinfections in the development of lymphoproliferative pulmonary disease in HIV, including with Epstein–Barr virus, cytomegalovirus and human T-lymphotrophic virus 1.

Since the advent of HAART, both LIP and NSIP seem to be less common in persons living with HIV, again emphasizing the importance of immune dysregulation in the development of both diseases. However, the widespread use of ART has brought with it the rise of other HIV-related ILDs, likely as a result of immune reconstitution. Reports of sarcoidosis, a disorder of unknown etiology that is characterized by granulomatous inflammation and a CD4+ alveolitis, were almost nonexistent pre-HAART but are now found with some regularity in the literature. The most commonly invoked explanation for the change in epidemiology is the development of immune reconstitution inflammatory syndrome (IRIS) in patients started on ART. IRIS is thought to result from the over-exuberant response of a previously dampened immune system to a host of previously recognized antigens or subclinical infections. Clinical data suggesting that sarcoidosis most often occurs when the CD4 count exceeds 200 cells/μL supports the role of IRIS in its development.

Other ILDs have been noted in persons living with HIV in the post-HAART era, including cryptogenic organizing pneumonia (COP) and hypersensitivity pneumonitis (HP). COP has been associated with P. jiroveci pneumonia and is also thought to represent a manifestation of IRIS. Similarly, HP, which results from a disordered CD8+ inflammatory response to an extrinsic allergen, was rarely if ever seen in the pre-HAART era. With the advent of HAART, it has been described in HIV-infected individuals exposed to a number of agents, notably efavirenz and bleomycin.

Clinical Presentation

Most of the ILDs described in HIV-infected individuals present in a similar fashion. Dyspnea and cough, which are typically subacute in duration, are frequently described along with low-grade fevers. Individuals presenting with LIP as a manifestation of underlying diffuse infiltrative lymphocytosis syndrome frequently show other features commonly seen in Sjögren’s syndrome such as xerostomia (“dry mouth”) and xerophthalmia (“dry eyes”). Presentations of sarcoidosis vary widely depending on the involved organ systems. All of these diseases may be accompanied by other systemic symptoms, such as fatigue and weight loss. On examination, fine inspiratory crackles are often present, but their absence does not rule out the presence of significant disease. Physical examination in sarcoidosis and LIP will again vary depending on the involved organ systems, but attention should be paid to lymphadenopathy and hepatosplenomegaly.

Laboratory data are often nonspecific and are not typically useful in making a discrete diagnosis. For example, in most cases, there will be an increased alveolar-arterial oxygen gradient on arterial blood gas analysis. However, the CD4 count itself may offer some etiologic clues. As discussed above, HP and sarcoidosis will frequently present after the initiation of ART and usually only when the CD4 count rebounds above 200 cells/μL. In contrast, COP has been described at variable CD4 levels in the setting of ART initiation. Although in most cases of ILD there will be evidence of interstitial infiltrates on chest imaging, chest radiographs can be normal, particularly in NSIP, although NSIP is typically associated with ground glass opacities and fibrosis (Figure 1A). The presence of bilateral hilar adenopathy in association with parenchymal abnormalities is highly suggestive of sarcoidosis. HP often appears with bilateral nodules, whereas COP usually presents as a focal consolidation. On computerized tomography (CT) scans, the majority of individuals will have ground glass opacities, with the exception of those with COP. Honeycombing, a radiographic sign that reflects relatively severe fibrosis, is usually only seen in advanced cases of sarcoidosis and HP. Honeycombing can also be seen in LIP, which is also associated with so-called “tree-in-bud”
opacities and peribronchial cuffing (Figure 2A). The bronchoalveolar lavage fluid in many of these diseases typically reveals a lymphocytic alveolitis, and flow cytometric analyses to determine if there is a CD4+ or a CD8+ predominance can help narrow the differential diagnosis. In contrast, a significant percentage of eosinophils in the lavage fluid (usually >10%) may be seen in drug-induced HP. As some infections may mimic ILDs, it is incumbent on the clinician to rule out occult infection. In the relatively unique context of IRIS, the exuberant inflammatory response in the lung may in fact be in the presence of a known pathogen such as M avium complex. In most cases of ILD, pulmonary function tests reveal a decrease in the diffusing capacity for carbon monoxide and a restrictive lung defect with relatively preserved airflows. However, airflow limitation may be present in sarcoidosis, HP and LIP. Pathologic specimens will usually demonstrate granulomas in patients with HP and sarcoidosis, whereas diseases on the spectrum of lymphocytic proliferation (NSIP, LIP, etc.) will show varying degrees of lymphocyte infiltration in the interstitium and within the alveolar spaces (Figures 1B and 2B). In contrast, COP will appear as an organizing pneumonia on histologic examination.

Treatment

As discussed above, NSIP and LIP are manifestations of immune dysregulation and are seen much less frequently in the current ART era. HIV-related NSIP is frequently self-limiting and rarely requires specific therapy. Stability or resolution of LIP has been described with corticosteroids, but there is as yet no standardized dosing or duration schedule given the infrequency of the disease. HP will frequently resolve completely after discontinuation of antigen exposure, although severe cases may require treatment with corticosteroids as well. Sarcoidosis rarely requires specific treatment either because most cases will spontaneously remit. Steroids can be considered in patients with an acute presentation but should be tapered promptly to avoid the effects of further immune compromise in these already vulnerable individuals.

Part 3: HIV-Related Pulmonary Hypertension

Pulmonary hypertension (PH), defined by a mean pulmonary arterial pressure ≥25 mm Hg at rest when measured directly by right heart catheterization (RHC), is classified into 5 different groups on the basis of underlying etiology and comorbid conditions. Group 1 PH, also known as pulmonary arterial hypertension (PAH), includes idiopathic disease, portopulmonary hypertension (ie, PH associated with cirrhosis and portal hypertension), pulmonary veno-occlusive disease and human immunodeficiency virus–related pulmonary arterial hypertension (HRPAH). Although the mechanisms of the association with HIV are not fully understood, PAH is now recognized as a complication of living with HIV. It was first described in 1987 in a 40-year-old man with a plexiform pulmonary vasculopathy. Since then, several studies have attempted to ascertain the true prevalence of the disease. As is true for many conditions associated with PH, the exact prevalence of PAH in patients with HIV is widely variable depending on the modality used to screen the population, specifically transthoracic echocardiography (TTE) versus RHC. Using TTE, 1 study reported a figure of 0.5% in 1991 based on a cohort of 1,200 subjects. Another cohort of more than 7,000 individuals living with HIV in France used an algorithm that screened patients with unexplained dyspnea using TTE and proceeded to RHC if the tricuspid valve regurgitant velocity was more than 2.5 m/s (reflecting possible PH to a degree that produces tricuspid valve regurgitation). They reported a prevalence of 0.46%, roughly similar to the figure reported by the prior cohort. A cross-sectional study found a higher prevalence of HRPAH in women than men (ratio of 1.4:1) when TTE was used to estimate pulmonary artery systolic pressures. Two more recent studies, both performed in Spain, found higher rates of HRPAH than have been previously reported: one found a prevalence of 2.6% in an asymptomatic cohort of HIV-infected individuals and the other found a rate of 10%. Of note, both studies used TTE to screen their populations, and as reported by others, TTE overestimates the presence of true PH confirmed by direct catheter measurements and does not provide an accurate assessment of pulmonary vascular pressures. However, even if the incidence of significant PH in persons living with HIV is assumed
to be approximately 0.5%, this represents a relative risk of almost a 1,000-fold compared with the general population.

As is the case with many diseases associated with PAH, survival in HRPAH is worse than in HIV alone. Data from a Swiss cohort demonstrated a survival rate of 21% at 3 years, which was significantly worse than the prognosis for those individuals living with HIV who did not have PH.63 More recent data from a French cohort showed a survival rate of 72% at 3 years, with cardiac function and CD4 counts both independently predictive of mortality.64

**Pathogenesis**

A number of mechanisms have been elucidated in the pathogenesis of HRPAH, but a conclusive picture has yet to emerge. Inflammation, genetics, intravenous drug use, coinfections and viral proteins themselves have all been implicated. The HIV-related protein gp120, which circulates in infected individuals and is the protein detected in screening tests for HIV infection, has been shown to target pulmonary endothelial cells and increase secretion of endothelin-1, a potent vasoconstrictor.65 Another HIV-related protein, negative factor (Nef), has been shown to infect endothelial cells in both humans and animals with HRPAH.66 In addition, bone morphogenic protein receptor 2 (BMPR-2), which has been implicated in cases of familial PAH not associated with HIV infection, is suppressed by the HIV transcriptional transactivator protein (Tat).67,68 Furthermore, the combination of viral proteins and hypoxia has been shown to synergistically increase the pulmonary artery pressures in a transgenic animal model.69 Hypoxia inducible factor 1α (HIF1α) seems to mediate the response to the viral proteins gp120 and Tat.70 Coinfection with human herpes virus 8 (HHV8) may also play a role as the virus has been found in plexiform lesions of patients with PAH,71 albeit not consistently in patients with HRPAH.72–74 Chronic inflammation has also been implicated, with rising levels of inflammatory markers associated with increasing pulmonary artery systolic pressures and tricuspid regurgitant velocities.75 In addition, drug use has been shown to potentiate the development of HRPAH in laboratory models.76

**Clinical Presentation**

As discussed above, the prevalence of elevated pulmonary vascular pressures seems to be increased even in asymptomatic HIV-infected individuals. However, to date, there are no specific clinical guidelines on the screening of patients with HIV for PH, and this is likely due to the relatively low overall prevalence of the disease. Individuals with HRPAH often come to clinical attention when they complain of nonspecific symptoms, including progressive dyspnea, chest pain and syncope, particularly as the disease progresses.77 Characteristic findings on physical examination include a loud pulmonary component of the second heart sound, a right ventricular heave, a murmur of tricuspid regurgitation, peripheral edema and ascites. Chest radiographs often reveal cardiomegaly and enlargement of the pulmonary arteries, whereas electrocardiographic evaluation will frequently show right atrial and ventricular enlargement with right axis deviation. TTE findings are consistent with those of the electrocardiogram and typically show pathologic enlargement of the right ventricle and right atrium and an increase in tricuspid regurgitation. However, as previously discussed, the estimated pulmonary pressures from the TTE can overestimate the true pressures in both HIV-infected and uninfected individuals.62,78 Therefore, when the clinical presentation and TTE findings are strongly suggestive of significant PH, most experts recommend RHC and direct measurement of pulmonary arterial pressures to confirm the diagnosis of HRPAH. Histologic examination is not necessary to confirm the diagnosis, but when performed typically reveals the plexiform vasculopathy characteristic of PAH (Figure 3).

**Treatment**

Treatment for HRPAH is mainly derived from studies on PAH in general because few rigorous studies on the treatment of HRPAH have been performed. The specific benefit of ART to decrease the levels of circulating HIV-related proteins is unclear in this setting; a small clinical study showed no hemodynamic benefit whereas there is experimental evidence in animal models that protease inhibitors decrease PH79 and at least 1 cohort study suggested that ART improved mortality in HRPAH.80 However, as current guidelines recommend ART for all HIV-infected individuals regardless of CD4 count or viral load, its specific role in the treatment of HRPAH may be moot. As a cautionary note, ART may interact with other specific PAH therapies and therefore the management of this complication can be particularly challenging.

Other therapies for the treatment of HRPAH include supplemental oxygen as hypoxemia is well known to exacerbate pulmonary vasoconstriction. Diuretic therapy is also used to mitigate the sodium retention caused by the right heart failure and is titrated to maintain right-sided filling pressures as near to normal as possible. Anticoagulation with warfarin is also recommended for all patients with PAH, with a target International Normalized Ratio (INR) of 1.5 to 2.5, as pulmonary arterial thrombosis in situ hastens the progression of the pulmonary arteriopathy. Calcium channel blockade can be considered in patients with a favorable response to vasoreactivity testing. Phosphodiesterase inhibitors, such as sildenafil, have been used in PAH with good results, but interactions with ART have limited their use in HRPAH81 and therefore this combination

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*FIGURE 3. Hematoxylin and eosin–stained section from an open lung biopsy in a patient with HIV shows the classic pathologic feature of pulmonary arterial hypertension; namely, the plexiform lesions that occlude blood flow within remodeled pulmonary arteries (arrow points to a typical plexiform lesion). Image provided by courtesy of Dr. Anthony Gal.*
requires careful monitoring. 82 In parallel, small studies examining the efficacy of bosentan, an endothelin receptor antagonist, suggest positive effects on several clinical parameters of HRPAH. 83,84 Other endothelin receptor antagonists have not been studied specifically in HRPAH, but they have shown efficacy in larger studies of PAH that included patients with HRPAH. 57 In addition, prostacyclin analogs such as epoprostenol, which are commonly used in severe PAH, have not been rigorously studied in HRPAH but seem to be effective based on the limited available data. 86 Overall, there is a relative paucity of rigorous clinical trials to guide recommendations for treatment in HRPAH. However, a systematic review of HRPAH suggested a significant benefit to specific PAH therapy, 87 and future studies will likely refine the therapeutic strategies for this relatively uncommon but devastating complication of HIV.

Part 4: HIV-Related Pulmonary Malignancies

Broadly speaking, lung malignancies in HIV-infected patients can be divided into AIDS-defining malignancies (ADM) and non–AIDS-defining malignancies (NADM). As a category, ADM includes Kaposi’s sarcoma (KS) and non-Hodgkin’s lymphoma (NHL). NADM refers to other primary lung cancers that have an increased incidence in HIV-infected individuals compared with uninfected individuals but do not define a transition from HIV infection to AIDS. The relative increased risk for lung malignancy conferred by HIV infection has been difficult to quantify, given the high prevalence of tobacco use in this population that confounds epidemiologic assessments. 88,89 Several studies have shown an increased risk of lung malignancy in the HIV-infected population, 80,81 with many experts now believing HIV to be an independent risk factor. This risk is likely to be more clearly validated as the population with HIV lives longer. In contrast, since the advent of HAART, the ADMs have decreased significantly in incidence. This almost certainly reflects the role of immunosuppression and coinfections in their development.

Pathogenesis

The 2 major ADMs seem to be related to both immunosuppression and coinfections. The incidence of KS, which is caused by infection with HHV8, is associated with the degree of immunosuppression and therefore is now far less common in the ART era. 92 It has also been associated with IRIS in a presentation known as a KS flare, presumably reflecting previous infection with HHV8. 93-95 KS behaves like an angioproliferative tumor that grows in response to a range of cytokines and growth factors, including IL-1, IL-6, tumor necrosis factor-α, and vascular endothelial growth factor. 96 HIV-related viral proteins, such as Tat, can also promote KS growth, 97 and HHV8 likely further potentiates this growth by an anti-apoptotic mechanism. 98

NHL has several different manifestations in HIV-infected individuals, including Burkitt’s lymphoma and diffuse large B-cell lymphoma. Epstein-Barr virus is frequently associated with NHL in HIV infection, as is the degree of immunosuppression. 99 Burkitt’s lymphoma involves translocation of the c-Myc gene, a key regulator of cell proliferation. Although less frequent than in cases of KS, NHL has also been associated with IRIS, 100 again highlighting the importance of coinfection in its pathogenesis.

HIV-infected individuals develop pulmonary NADM at higher frequencies than that of the general population 101 even after the advent of HAART. 102 In recent studies, lung cancer continues to be the most common NADM, 103 and this risk seems to be tied to the level of immunosuppression 104 although tobacco use is a significant confounder. Some have speculated that previous infections and chronic inflammation may also play a role in conferring an increased risk of lung cancer in individuals with HIV, 105 although the molecular mechanisms remain to be elucidated.

Clinical Presentation

As discussed above, pulmonary KS typically presents in HIV-infected individuals who have relatively low peripheral CD4 counts. 106 It is most often associated with cough, dyspnea and fever; these symptoms do not distinguish it from opportunistic infections. Chest radiographs most often show bronchial wall thickening and nodules, whereas computed tomography often shows numerous nodules, tumor masses, bronchial wall thickening and/or bilateral pleural effusions. 107 In the setting of IRIS, KS flares have similar findings, including reticular and reticulonodular opacities, consolidation and effusions. 108 CT scans often reveal flame-shaped infiltrates extending outward from the hila into the lung parenchyma along the bronchovascular bundles (Figure 4A). The appearance of ground glass opacities can also be seen on CT scan but should trigger a search for concomitant opportunistic infections. Importantly, although pulmonary KS is usually associated with clinically apparent mucocutaneous involvement, a significant percentage of patients with pulmonary KS will not have visible lesions on skin examination and therefore the clinician must maintain a high level of suspicion in the appropriate clinical context. At bronchoscopy, KS lesions characteristically appear as purple or red macules, often at airway bifurcations, 109 but may be missed if they do not involve the airway directly or are too distal to be visualized. Histologically, KS is diagnosed by its characteristic spindle cells and high vascularity (Figure 4B).

Patients with AIDS-related NHL frequently present with cough, dyspnea and constitutional symptoms. 110 Physical examination often demonstrates tachypnea, crackles, lymphadenopathy and hepatomegaly. Most have advanced HIV, with low CD4 counts increasing the likelihood of the disease. Elevated sedimentation rates and serum levels of lactate dehydrogenase levels are also commonly seen. Chest radiography most often reveals consolidation, nodules, reticular infiltrates or masses. Pleural effusions can also be seen but less commonly so. On computed tomography, a cardinal feature is intrathoracic lymphadenopathy. The diagnosis in made by transbronchial biopsy or endobronchial ultrasound-guided sampling of mediastinal lymph nodes or by pleural fluid cytology when effusions are large enough to sample. Surgical lung biopsy has a high diagnostic yield and may be necessary if other less invasive studies are nondiagnostic, but it is obviously associated with greater morbidity.

NADMs of the lungs present similarly in HIV-infected and uninfected individuals, although those with HIV tend to be younger, with a mean age at diagnosis of approximately 48 years as compared with approximately 60 years in the non–HIV-infected population. 110 although at least 1 study suggests that the age difference may not be so large between the 2 populations. 111 Most studies evaluating NADMs in the lung have found adenocarcinoma to be the most common cancer type. 112 Unfortunately, HIV-infected individuals tend to present with more advanced disease, 113 although their mortality seems no higher than the uninfected population if staging is taken into account. Interestingly, most individuals have a CD4 count greater than 200 cells/μL at the time of diagnosis.

Treatment

KS is primarily treated with ART, which has been shown to cause regression of KS lesions. As noted above, however, KS flares have been described in the setting of ART initiation and merit particular attention. In patients who do not respond to ART, chemotherapy and radiotherapy have been used with
good success, provided the treatments can be tolerated.\textsuperscript{114–116} However, KS remains a serious complication and the presence of pulmonary KS significantly increases mortality.\textsuperscript{92}

NHL in the HIV-infected patient is usually treated with chemotherapy. As discussed previously, ART plays an essential role in preventing the development of NHL. For relatively refractory cases, high-dose chemotherapy and autologous stem cell transplantation have also been used.\textsuperscript{117}

For prevention of NADMs, strong emphasis should be paid to the importance of smoking cessation. For those HIV-infected individuals identified with lung cancer who are not on ART, many clinicians favor initiating ART before starting chemotherapy in an effort to enhance their overall functional status. Special care must be taken to avoid interactions between chemotherapeutic agents and ART.\textsuperscript{118} However, there are at present no specific guidelines for the treatment of HIV-infected individuals with pulmonary NADMs and no specific recommendations regarding the screening of these individuals for pulmonary malignancy.

**SUMMARY**

Clinicians caring for individuals living with HIV must be aware of the wide range of noninfectious pulmonary diseases that can occur in this unique population, particularly as the prognosis has dramatically changed with the advent of effective ART. Cohort studies indicate that many of these diseases occur with less frequency in the era of ART, but other diseases that were virtually nonexistent before the availability of effective anti-retroviral drugs are now coming to the fore. Laboratory studies offer insights into the pathogenesis of many of these processes, but much work remains to be done. From a clinical standpoint, pulmonary infections remain an important cause of morbidity and mortality and must be ruled out whenever possible. However, as people are now living much longer with HIV and the HIV-infected population ages, noninfectious pulmonary diseases are becoming more common and even more important to recognize.

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