Review Article

Bronchoscopy and Endobronchial Disease in Patients with Human Immunodeficiency Virus Infection

Toshita Kumar, Marcia Epstein, Yelena Markovskaya, Mangala Narasimhan, Mark Rosen and Arunabh Talwar

Division of Pulmonary, Critical Care and Sleep Medicine, North Shore-Long Island Jewish Health System, New Hyde Park, NY, USA

ABSTRACT

The natural history of human immunodeficiency virus (HIV) infection has been significantly altered since the advent of antiretroviral therapy (ART). However, lung diseases are still common in these patients. This makes flexible fibreoptic bronchoscopy a valuable diagnostic tool. Knowledge of the visual appearance of various diseases would be of utmost importance to the bronchoscopist. Timely recognition of the endobronchial appearance of these diseases can narrow the differential diagnosis and potentially mitigate an avoidable delay in the diagnosis.
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Key words: Bronchoscopy, HIV, Endobronchial patterns.

INTRODUCTION

The use of combination antiretroviral therapy (ART) has changed the spectrum and outcome of pulmonary disorders in patients with human immunodeficiency virus (HIV) infection. Despite the reduced incidence of opportunistic infections, however, lung diseases are still common in HIV infected patients.[1,2] These patients present with rather non-specific clinical and radiological patterns making and flexible fibreoptic bronchoscopy (FOB) has emerged as a valuable diagnostic tool in them. The safety and diagnostic yield of FOB and techniques such as bronchoalveolar lavage (BAL) in patients with acquired immunodeficiency syndrome (AIDS) who have lung disease is well established.[3,4] Even though endobronchial disorders are unusual, the endobronchial appearance of these lesions in conjunction with clinical presentation may facilitate establishment of the correct diagnosis.[5] Some lesions may require specific biopsy techniques or special stains. With the exception of pseudomembranous necrotising tracheobronchial aspergillosis, there are no specific endobronchial lesions associated with HIV infection which increase the risk of complications when biopsied. This article reviews the causes and bronchoscopic features of endobronchial lesions in patients with HIV infection to help bronchoscopists identify these lesions while performing FOB. The management aspect of these diseases in the setting of HIV infection and AIDS is beyond the scope of this review and will not be discussed.

KAPOSI's SARCOMA

Kaposi's sarcoma (KS) is a neoplasm seen almost exclusively in HIV-infected patients and is thought to be caused by human herpes virus-8 (HHV-8). The prevalence of KS has declined over the last two decades. Although intrathoracic KS is seen in up to 75% of patients with KS at a median time of 11 months from the time of diagnosis of cutaneous KS,[6] isolated pulmonary KS without cutaneous involvement is rare.[7] When pulmonary KS regresses after chemotherapy and ART, BAL fluid, HHV-8, deoxyribonucleic acid (DNA) may also become undetectable, suggesting that this is a highly sensitive and specific test.[8]

Reduced vital capacity and forced expiratory volume in the first second (FEV_1) correlate with the presence of endobronchial lesions.[9] Radiographically, these lesions most often present as multiple, ill-defined nodules. In contrast, the bronchoscopic appearance of KS is quite characteristic; the lesions appear as violaceous slightly raised lesions that easily bleed. Frequently, the lesions are described as erythematous plaque-like lesions that can be confluent and tend to occur in the proximal airways (Figures 1 and 2). Bleeding is an important complication and

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Correspondence and reprint requests: Dr Arunabh Talwar, North Shore-Long Island Jewish Health System, Division of Pulmonary, Critical Care, and Sleep Medicine, 410 Lakeville Road, Suite 107, New Hyde Park, NY 11010, USA; Phone: (516) 465-5400; Fax: (516) 465-5454 ; E-mail: Arunabh@nshs.edu

occurs in about 30% of endobronchial biopsies in pulmonary KS. The poor yield of biopsy (12%) is probably because of the submucosal location of the lesions. However, as the endoscopic appearances are typical and given the risk of bleeding, biopsy is usually not necessary for the diagnosis of pulmonary KS. The incidence of alveolar haemorrhage is also high in patients with pulmonary KS and is thought to be due to HHV-8 promoted angiogenesis and vascular permeability.[10] Thus, pulmonary KS should be strongly considered as a possible cause for respiratory illness in any patient with cutaneous KS.[11,12]

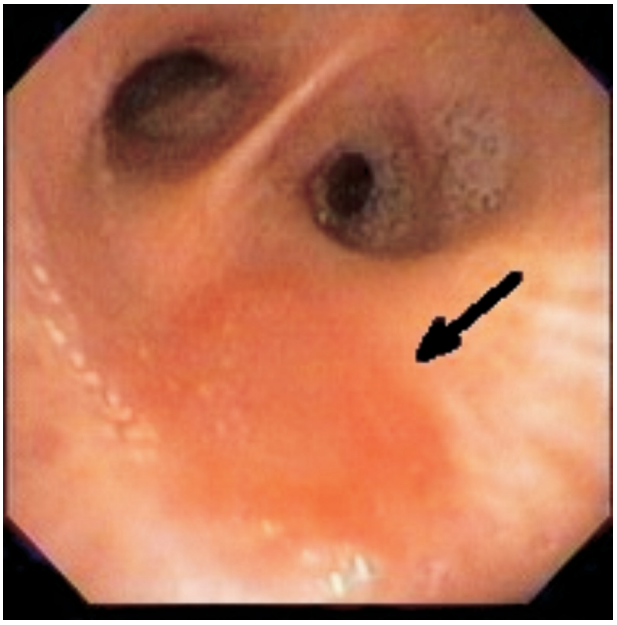

Figure 1. Bronchoscopic image showing violaceous slightly raised lesions of Kaposi's sarcoma (arrow).

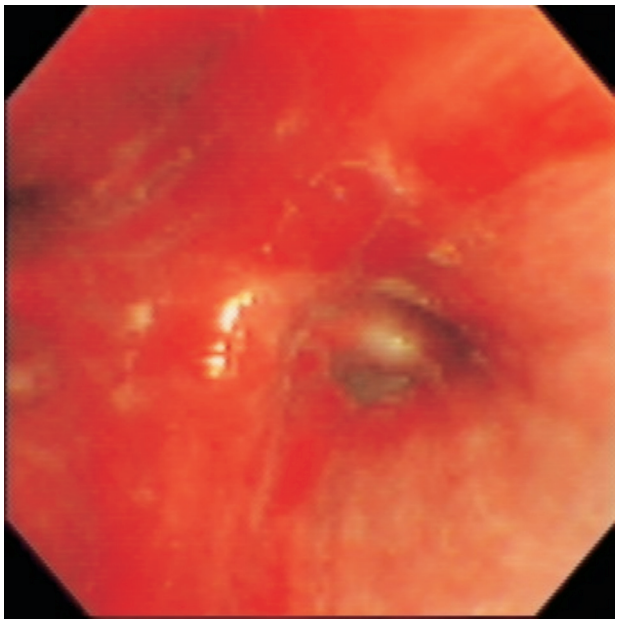

Figure 2. Bronchoscopic image showing violaceous slightly raised lesions of Kaposi's sarcoma.

LUNG CANCER

The incidence of lung cancer is increased in patients with HIV infection, even when smoking is taken into account. Increased susceptibility to lung cancer may be due to HIV-induced abnormal immune surveillance, particularly by natural killer cells, as well as by stimulating the release of aberrant growth factors resulting in oncogenesis.[13,14]

Lung cancer is the most frequently diagnosed non-AIDS-defining malignancy and a 3.5-fold elevated risk for lung cancer associated with HIV infection has been documented.[15] Predominance of adenocarcinoma has been described.[16] Lung cancer is clearly associated with smoking and other behaviours such as intravenous drug use which results in drug-induced changes in the pulmonary stroma.[17] The CD4+ cell count and viral load are also prognostically significant. Lung cancer in HIV-infected individuals presents in younger individuals, at a later stage, and has a poorer prognosis with median survival of only four weeks to three months. For this reason perhaps, young patients with lung cancer should routinely have HIV testing. It is also possible that lung cancer diagnosis is delayed as pulmonary nodules in this population are often felt to have an infectious aetiology. The endobronchial appearance of lung cancer is similar to that observed in patients without HIV infection. However, in young patients with HIV presenting with submucosal nodules on bronchoscopy, a high index of suspicion for lung cancer should be maintained (Figures 3 and 4).

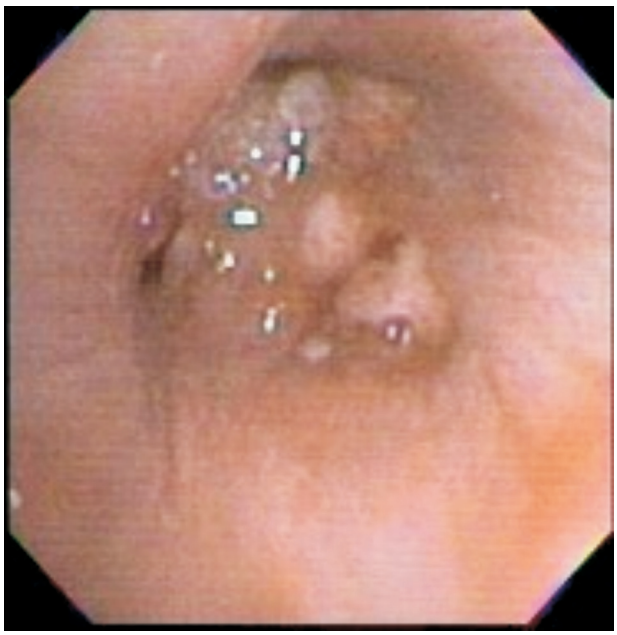

Figure 3. Bronchoscopic image showing endobronchial involvement of non-small cell lung cancer.

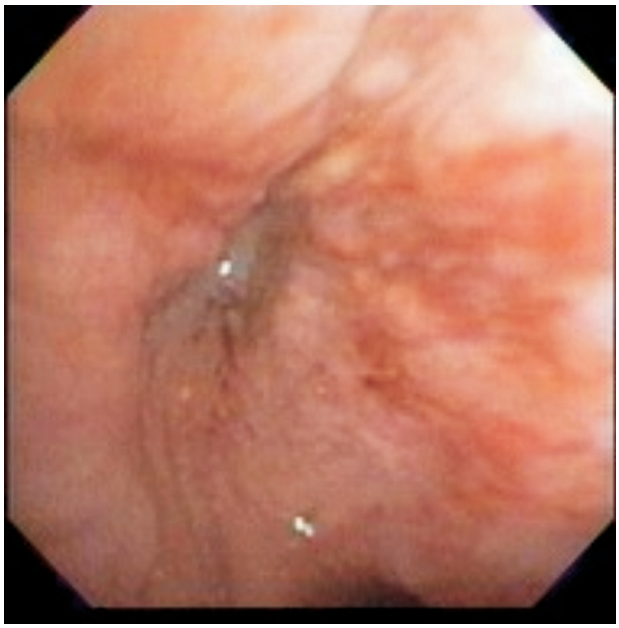

Figure 4. Bronchoscopic image showing endobronchial involvement of small cell lung cancer.

BACILLARY ANGIOMATOSIS

The incidence of bacillary angiomatosis (BA) has declined with the use of ART, and is now seen only in patients with highly advanced HIV infection. It is caused by *Bartonella henselae* and usually presents with a skin rash and non-specific symptoms. Involvement of the liver, spleen and bones is common. Pulmonary BA with or without cutaneous lesions has been described. Slater and Min[18] reported a case in which polypoid endobronchial lesions with recent fever, skin lesions, lymphadenopathy, pulmonary infiltrates and effusions were the presenting signs of BA. Finet *et al*[19] describe BA presenting as a large solitary right-sided thoracic mass involving the intercostal space and the posterior chest musculature along with hilar lymphadenopathy and cutaneous lesions closely resembling KS. The mass was resected and the cutaneous lesions responded to erythromycin.

Interestingly, skin and endobronchial lesions of BA appear similar to those of KS. Therefore, this easily treatable condition often remains unrecognised.[20] It is suggested that in symptomatic patients presenting with bronchoscopically characteristic KS lesions but without biopsy confirmation, a trial of macrolides or doxycycline may be attempted. If a good response is observed on repeat FOB, the diagnosis of BA may be inferred and oral doxycycline should be continued.[21]

LYMPHOMA

The overall frequency of lung involvement in patient with HIV-associated lymphoma is estimated to be 5.7% to 5.8%, underscoring why endobronchial lesions from lymphomas are rare.[22,23] Pulmonary manifestations of non-Hodgkin's lymphoma (NHL) include pleural effusions, lobar consolidations, nodules, reticular infiltrates or masses.[24] The FOB and transbronchial lung biopsy can help in the diagnosis.

Primary pulmonary lymphoma (PPL) is very rare occurring mainly in patients with profound immunosuppression (mean CD4+ T-lymphocyte count 17/μL). Time lag from HIV-seropositivity to PPL is usually five years (range 1-8 years). Contrary to disseminated NHL, the levels of lactate dehydrogenase (LDH) are only mildly elevated (mean of 1.5 times normal) in PPL. The most common radiographic findings are well-defined rapidly growing subpleural nodules.[25]

Cadranel *et al*[26] defined the role of FOB in the diagnosis of PPL. The BAL fluid shows a lymphocytic alveolitis (≥20% lymphocytes) in two-thirds of the patients. Lymphocytosis can be considered specific for lymphoma if at least 10% of lymphocytes are B-cells, and the clonal nature of these cells can be demonstrated. The close association of Epstein-Barr virus (EBV) and B-cell monoclonality in lung tissue is now well established. Latent EBV infection, which is of unknown prognostic significance in PPL, can be evaluated by latent membrane protein expression by immunohistochemistry (IHC) and by *in-situ* hybridisation (ISH).

Of note, EBV is associated with other endobronchial tumours in AIDS patients. Blumh *et al*[27] reported a case of endobronchial lesions from multicentric smooth muscle tumours. Diffuse EBV gene expression in the tumour tissue supports the hypothesis that EBV infection contributes to the pathogenesis of tumours of smooth muscle origin in immunocompromised hosts.

TUBERCULOSIS

Globally, the most common lung infection in patients with HIV-infection is tuberculosis (TB). Tuberculosis becomes more common with decreasing CD4+ T-lymphocyte counts.[28] The pathogenesis of endobronchial TB (EBTB) is not fully established.[29] Hypotheses proposed involve direct implantation of the bacilli into the bronchus from adjacent pulmonary parenchymal lesions, direct airway infiltration from adjacent mediastinal lymph node TB, erosion and protrusion into the bronchus of intrathoracic TB lymph nodes, haematogenous spread, and extension by lymphatic drainage.[30]

Lee and Chung[31] reported the following patterns of EBTB in 114 patients: actively caseating, oedematous-hyperaemic, fibrostenotic, tumourous, granular, ulcerative, and non-specific bronchitic. These seven subtypes are believed to be the consecutive stages of the development of EBTB. Their prompt recognition and timely therapy can prevent and reduce bronchial narrowing which will promote drainage and decrease lung damage.[32] Rarely, these endobronchial lesions can mimic bronchogenic carcinoma (Figure 5).[33]

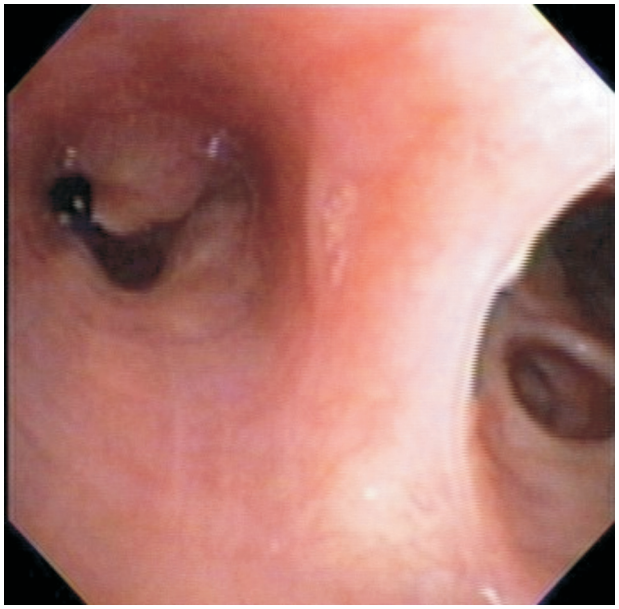

Figure 5. Bronchoscopic image showing endobronchial lesion of tuberculosis.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune reconstitution inflammatory syndrome (IRIS) is a manifestation of increased immune activity usually in response to ART. Clinically and radiographically, AIDS patients with TB and other diseases such as sarcoidosis, cytomegalovirus (CMV) and *Mycobacterium avium* complex (MAC) infection can paradoxically worsen after the initiation of ART.[34-38] Symptoms of weight loss, fever, cough, new infiltrates and mediastinal and hilar lymphadenopathy usually appearing four to six weeks after starting ART suggest the diagnosis of IRIS. The treatment of IRIS is usually supportive, and at times may require administration of corticosteroids.[39]

In patients with pulmonary MAC disease, IRIS presents as raised submucosal endobronchial lesions that can lead to total or partial airway obstruction. These lesions are commonly multifocal and bilateral.[40] Immune reconstitution inflammatory syndrome can also cause worsening of EBTB lesions. Narita *et al*[41] compared patients with TB and HIV who received both ART and antituberculosis (ATT) therapy with patients with TB only who received ATT only. Patients who received ART and ATT experienced worsening of the symptoms and EBTB lesions significantly more than patients treated with ATT only. Other significant mechanical complications in the airways include bronchial obstruction by tumorous lesions, bronchial stenosis, or airway perforation by ulcerative lesions (Figures 6 and 7).

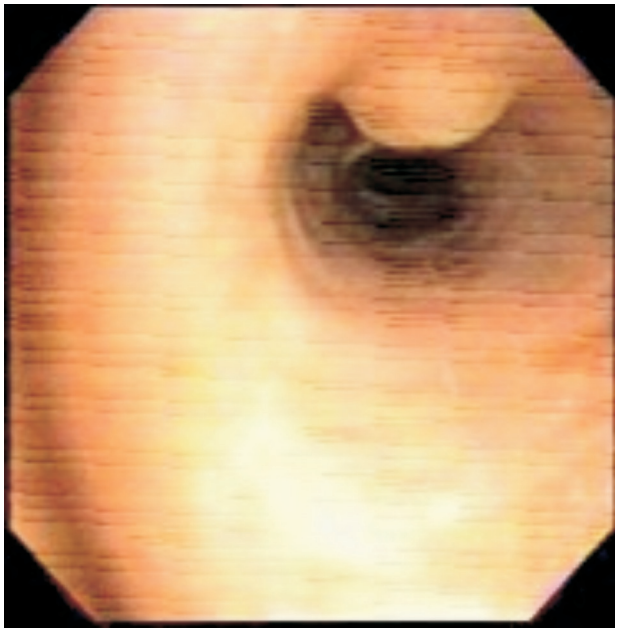

Figure 6. Bronchoscopic image showing raised submucosal endobrochial lesion of immune reconstitution inflammatory syndrome secondary to *Mycobacterium avium-intracellulare*.

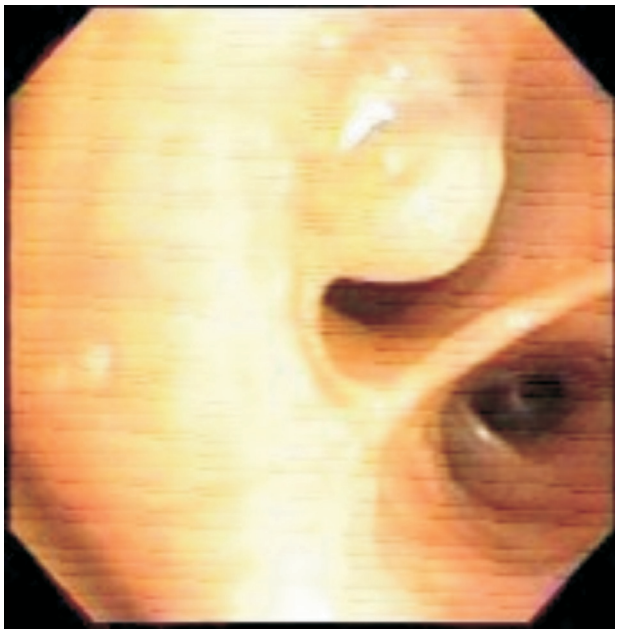

Figure 7. Bronchoscopic image showing raised submucosal endobrochial lesion of immune reconstitution inflammatory syndrome secondary to *Mycobacterium avium-intracellulare*

ATYPICAL MYCOBACTERIA

Mycobacterium avium complex is a common opportunistic infection due to non-tuberculous mycobacteria (NTM) in HIV-infected patients and commonly presents with disseminated disease. It rarely presents with invasive pulmonary disease limited to the chest.[42] Endobronchial lesions, also reported with other NTM infections, are also rare and occur regardless of immune status and generally regress with medical treatment.[43-45]

CRYPTOCOCCUS NEOFORMANS

Cryptococcus neoformans is a common opportunistic pathogen in HIV-infected patients with CD4+ T-lymphocyte counts below 100/μL. It is an encapsulated yeast inhaled from environmental sources that stains best with the Indian ink preparation. Cryptococcosis generally presents with disseminated infection in end-stage AIDS patients. Pulmonary manifestations and meningitis are prominent while other organ involvement tends to be clinically silent mandating a search for extra-pulmonary infection in HIV-positive patients with pulmonary cryptococcosis. Endobronchial mass lesions, plaques, ulcerations and pseudomembranes may occur, but all of these are uncommon.[46-48] These non-specific appearances of endobronchial disease necessitates diagnosis by identifying the yeast.

CYTOMEGALOVIRUS

Human CMV can infect virtually any tissue but clinically is almost always asymptomatic. In immunocompromised persons, CMV disease may take the form of retinitis, oesophagitis, colitis, hepatitis, pneumonitis, and encephalitis, among others. As opposed to immunosuppression following transplantation, CMV pneumonitis is unusual in HIV disease. Cytomegalovirus-related necrotising tracheitis can cause severe central airway obstruction, with characteristic intranuclear and intracytoplasmic inclusions and positive cultures.[49] Cytomegalovirus infection of the upper airway should be considered in patients with AIDS presenting with atypical cough or stridor and ulcerated endobronchial lesions.

The diagnosis of CMV-related disease depends on identification of typical viral inclusions in a patient who has disease without alternative explanation since the virus may be found in tissues and body fluids of asymptomatic persons.[50] Other diagnostic modalities for active infection include polymerase chain reaction (PCR) and quantitative assays. However, this may also indicate or predict the development of CMV disease at another site.

PULMONARY ASPERGILLOSIS

Despite being a very common pathogen in neutropaenic and other immunocompromised patients, aspergillosis is relatively uncommon in HIV patients. However, with CD4+ T-lymphocyte counts <50/μL, HIV patients may develop pulmonary aspergillosis. Cough and potentially fatal haemoptysis are the most common presenting symptoms. Progression to more invasive disease occurs in up to 50% of HIV-infected patients and carries a poor prognosis. Antifungal treatment should, therefore, be initiated as soon as possible.[51]

Endobronchial presentations may include necrotising, ulcerative or pseudomembranous tracheobronchitis.[52] This type of infection can progress to transmural necrosis of the airways, tracheal perforation or invasive aspergillosis (Figure 8).[63] Lesions may appear as small exophytic lesions, multiple (2-5mm) inflammatory ulcers, some blackened and necrotic, some coated with a shaggy fibrinous exudate, and some cream-coloured plaques.[53,54] Aspergillomas have been reported in pre-existing cavities, often from prior *Pneumocystis* infection, usually without tissue invasion.[55,56] Others have reported atelectasis presumed due to airway obstruction with fungal casts occluding the central airways leading to airway compromise.[54]

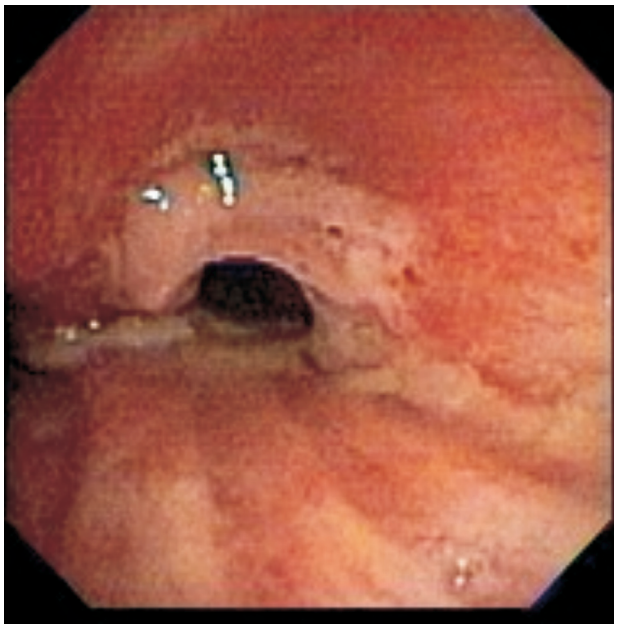

Figure 8. Bronchoscopic image showing pseudomembrane due to aspergillosis.

CONCLUSIONS

Lung is the most common site of complications of HIV disease, most of which are infectious. In some instances, the airways are affected and these

patients often present with typical features of endobronchial involvement. Lung cancers are occurring with increased frequency in HIV-infected persons. Additionally, endobronchial infectious diseases occur predominantly in these patients with advanced immunosuppression. Timely recognition of the endobronchial appearance of these diseases can narrow the differential diagnosis and potentially mitigate an avoidable delay in diagnosis. Therefore, familiarity of the clinician with endobronchial manifestations of various complications of HIV may impact morbidity and mortality of these patients.

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