

Human immunodeficiency virus infection and pneumothorax

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Abstract: Pneumothorax is a serious and relatively frequent complication of human immunodeficiency virus (HIV) infection that may associate with increased morbidity and mortality and may prove difficult to manage, especially in patients with acquired immunodeficiency syndrome (AIDS).

Keywords: Human immunodeficiency virus (HIV); infections; virus

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Introduction

Spontaneous pneumothorax occurs 450 times more frequently in patients with acquired immunodeficiency syndrome (AIDS) versus the general population and is now the leading cause of nontraumatic pneumothorax in the urban population, to include both those with and without AIDS (1). At some medical centers, more than 50% of patients with spontaneous pneumothorax have AIDS (2). The incidence of spontaneous pneumothorax in human immunodeficiency virus (HIV)-seropositive individuals is estimated to be about 2-5% of overall total cases (3-6). Immune status seems to influence this incidence, as it is related to the appearance of opportunistic lung infections, which are favored by the immunodeficiency. In a 3-year period study of 599 HIV-infected patients by Afessa *et al.*, pneumothorax developed in 1.2% of hospital admissions (3), while in a recent observational study by Rivero *et al.*, over 105 HIV-seropositive patients with spontaneous pneumothorax, the incidence of this complication in non-treated HIV-infected patients was estimated to be 1.06% (4).

HIV-infected patients who develop pneumothorax

have a bad prognosis (5) and the mortality rate associated with this complication varies from 30-60%. Afessa *et al.* reported an in-hospital mortality of 30.8% compared to 5.8% of those without pneumothorax ($P=0.0060$) (3), while in a small case series by Golpe Gómez *et al.* the mortality rate was estimated to be 66% among patients with HIV and pneumothorax, with a mean survival time of 55.6 days (7).

Aetiology

As in other circumstances, pneumothorax in HIV-infected individuals can be categorized as primary, secondary and iatrogenic or traumatic according to aetiology.

Primary

Primary spontaneous pneumothoraces can occur in HIV-seropositive patients with no predisposing lung disease or history of thoracic trauma. In the majority of cases they commonly occur in young, tall, thin males with current cigarette smoking. The rupture of an underlying subpleural bleb or bulla is thought to be responsible in many cases.

Secondary

Secondary pneumothoraces occur when there is an underlying abnormality. *Pneumocystis jiroveci* infection and infections by other pulmonary microorganisms are the leading causes. In a case series of 25 consecutive patients with AIDS and pneumothorax reported by Byrnes *et al.*, all patients had a documented pulmonary infection (8). Nevertheless, with the introduction of highly active antiretroviral therapy (HAART), HIV has become a chronic disease and as HIV-infected patients are aging, they are at increased risk for other comorbid diseases—like pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, bronchiectasis or lung cancer—that can also predispose to the development of secondary pneumothorax.

The aetiology of spontaneous pneumothorax in HIV patients seems to be related to the patients risk practices and to their degree of immunosuppression. Thus, the most common cause among intravenous drug users and in patients with a CD4+ lymphocyte count of more than 200 cells/mL is bacterial pneumonia, and on the other hand, among sexually transmitted HIV-infected individuals and those with less than 200 cells/mL or with AIDS is *Pneumocystis jiroveci* infection (4).

Pneumocystis jiroveci infection

Pneumocystis jiroveci pneumonia is a common opportunistic infection affecting immunosuppressed patients and previous or active *Pneumocystis* infection appear to be a risk factor for developing of pneumothorax. Among radiological findings of *Pneumocystis jiroveci* pneumonia are cysts, pneumatoceles and spontaneous pneumothoraces (9). These findings require prompt differential diagnosis in HIV-seropositive patients with acute respiratory compromise as in rare instances *Pneumocystis* pneumonia can occur in cystic form and the correct diagnosis can be missed.

The incidence of pneumothorax in patients with current or previous *Pneumocystis jiroveci* infection is reported to be extremely high. Most patients with spontaneous pneumothorax and AIDS have *Pneumocystis jiroveci* infection and necrotic subpleural blebs (2). Ingram *et al.* reported that 86% of spontaneous pneumothoraces occurred in patients with acute or recent *Pneumocystis jiroveci* pneumonia, accounted for over one-half of all pneumothoraces, while 8% of the traumatic pneumothoraces developed in patients who did not have *Pneumocystis* pneumonia resolved (10). In another small case series by

Golpe Gómez *et al.*, *Pneumocystis jiroveci* infection was diagnosed in 66% of HIV-infected patients, either before or simultaneous to the appearance of pneumothorax (7), while in a recent observational study of Rivero *et al.*, *Pneumocystis jiroveci* accounts for 34.3% of all HIV-seropositives with spontaneous pneumothorax. Ingram *et al.* reported that HIV-infected patients who had pneumothorax as well as *Pneumocystis jiroveci* infection were more difficult to manage and had poorer outcome (50% mortality) than those who did not have *Pneumocystis* infection (25% mortality) (10). This is why, so far, many authors suggest that the development of pneumothorax in HIV-seropositive individuals should prompt a search for *Pneumocystis jiroveci* infection (11).

Except from *Pneumocystis jiroveci* infection *per se*, aerosolized pentamidine prophylaxis against *Pneumocystis jiroveci* infection used in HIV-seropositive patients, may predispose these patients to the development of pneumothorax. Since the introduction of aerosolized pentamidine for prophylaxis against *Pneumocystis jiroveci* infection, an increasing number of cases of atypical manifestations of infection with *Pneumocystis jiroveci* have been reported in the United States, like upper lobe pneumonia, extrapulmonary *Pneumocystis* infections and spontaneous pneumothorax, making the association between these atypical manifestations and the use of aerosolized pentamidine to seem very likely (12). Pneumothorax and extrapulmonary pneumocystosis were reported among serious events related to the use of aerosolized pentamidine (13), while many authors underlined the increased risk of pneumothorax due to recurrent apical infections with *Pneumocystis jiroveci* (14), which seemed to be independent of the aerosolized pentamidine use (15). One of the mechanisms proposed for this association is that bullous changes and pulmonary cysts develop in lung apices due to repeated episodes of inflammation and cytotoxic effects of HIV on pulmonary macrophages, leading to recurrent apical *Pneumocystis jiroveci* infection that progress despite prophylaxis with aerosolized pentamidine (14).

Other pulmonary infections

As concurrent HIV infection increases the susceptibility to bacterial and other opportunistic infections, many of these lung infections can be implicated to the development of pneumothorax in HIV-infected individual as causes of pulmonary cavitation. Among them is active pulmonary infection by *Mycobacterium tuberculosis*, which is reported to be an independent risk factor for pneumothorax (16). The

incidence of active or old tuberculosis infections among HIV-seropositives with pneumothorax is estimated to be from 15% (4) to 30% (7), depending the immune status of HIV-infected patients.

Among bacterial infections as causes of spontaneous pneumothorax in HIV-seropositives has been reported necrotizing pneumonias caused by *Pseudomonas aeruginosa* (5), *Salmonella spp.* (17), *Staphylococcus aureus* (18) and *Streptococcus pneumoniae* (19). In a recent retrospective review of HIV-positive patients with lung cavitation, bacterial pneumonia was found to be the most common cause of pneumothorax in non-treated HIV-infected patients (34.3%), especially in drug users (40%) and the most common cause of unilateral spontaneous pneumothorax (4).

Some fungal lung infections can, also, proceed to lung cavitation and spontaneous pneumothorax—like *Cryptococcus neoformans* and *Aspergillus fumigatus* (18)—and thus should be included in the differential diagnosis of pneumothorax and underlining pulmonary infection.

Iatrogenic or traumatic

Traumatic pneumothorax occurs following direct injury of the pulmonary parenchyma. Except central vein cannulation (more commonly subclavian) that is known to be a cause of pneumothorax, many iatrogenic invasive maneuvers used in a small subset of HIV-infected patients with undiagnosed diffuse or multifocal pulmonary disease—like transbronchial or open lung biopsy, fine needle transthoracic aspiration, surgical mediastinal exploration and occasionally pleural acupuncture—can be associated with the development of pneumothorax. In a study of Flaguera *et al.*, traumatic iatrogenic pneumothorax due to transthoracic needle aspiration in patients with HIV infection, reported to be up to 17%, but only on procedure resulted in a pleural drainage (20). Also, in a case series of Ingram *et al.*, over one-third of pneumothoraces in HIV-infected patients were attributed to trauma and 78% of these were caused by insertion of a catheter (10). The high incidence of pneumothorax after cannulation of the subclavian vein in HIV-seropositive patients could be explained by the frequent occurrence of an underlying diseased lung parenchyma and the poor performance status with severe dehydration, which requires a more demanding technique (6).

On the other hand, therapeutic interventions like the need of intubation and mechanical ventilation or noninvasive pulmonary ventilation, may prone HIV-infected patients

to development of pneumothorax due to barotrauma or volutrauma, which is associated with increased mortality and poor outcome (21).

Clinical presentation and diagnosis

The presentation of a pneumothorax varies among minimal pleuritic chest discomfort, mild dyspnea at rest and dry cough to a life-threatening rapidly progressive respiratory deterioration resulting in cardiorespiratory collapse. Even if acute respiratory distress in a HIV-infected patient has a broad differential diagnosis, spontaneous pneumothorax must always be added to the list of causes. The presence of pneumothorax can be confirmed by imaging studies, like chest radiographs or computed tomography imaging of the chest, when diagnostic uncertainty exists—for example to distinguish a pneumothorax from other cystic lung parenchymal changes. Nevertheless, the most important part in diagnostic evaluation in HIV-infected individuals with pneumothorax seems to be the early and prompt search for an underlying causative infectious disease.

Therapy

Pneumothorax associated with HIV-infection seems to be a difficult condition to treat successfully both for the pulmonary internist and the surgeon (22). This is mainly due to the fact that HIV-related spontaneous pneumothorax often is complicated by a virulent form of necrotizing subpleural necrosis, with a marked lung and pleural involvement in the inflammatory process, which makes the underlying lung parenchyma inflamed and friable, and results in failure of lung re-expansion and persistent air leaks that are refractory to the standard, traditional forms of therapy, necessitating surgical revision (22,23).

Spontaneous pneumothorax in HIV-infected patients seems to require longer drainage time for recuperation. Also, many authors report the frequent failure of the simple chest tube drainage, with a high rate of recurrence of lung collapse or persistence of air leak. In a small case series by Golpe *et al.*, although successful initial control of pneumothorax was achieved with simple drains in 58% of the episodes, the recurrence rate was 71% (7), while in another study of Carbera-Cordero *et al.*, a persistent significant air leak was present in 33.3% of patients (6). Of course, always must kept in mind that the outcome depends on whether HIV-infected patients have coexisting diseases, like *Pneumocystis jirovecii* infection. Ingram *et al.* reported that the management of

traumatic pneumothoraces in HIV-seropositive patients who did not have *Pneumocystis jiroveci* infection was uncomplicated, even if the duration of tube placement was greater than other non HIV-infected patients with iatrogenic pneumothorax. On the other hand, the traumatic pneumothoraces in patients with *Pneumocystis jiroveci* infection were more difficult to manage and were associated with 62% mortality (10). So, it is important all HIV-seropositives with pneumothorax to undergo a diagnostic evaluation and initiate empiric antimicrobial therapy for *Pneumocystis* infection if there is high suspicion.

Many studies suggest an aggressive stepped-care management to avoid more serious surgery in patients with high surgical risks.

Conservative approach

Patients with small pneumothoraces (less than 15-20%) may have spontaneous resolution, so they must remain under close observation or if they are symptomatic a conservative approach could be the attachment of a Heimlich valve to a small bore chest tube. In patients with larger pneumothoraces the treatment of choice is the application of a chest tube thoracostomy. If re-expansion is not achieved by tube thoracostomy patients will need therapy with videothoracoscopy for stapling and pleurodesis. Nevertheless, a conservative management option that may benefit patients with persistent air leak who are poor candidates for surgery could be bedside pleurodesis (installation through the thoracic drainage tube of talc or a chemical sclerosing agent, like doxycycline, tetracycline or bleomycin) (2). Heimlich valve can be used as another alternative conservative approach for the management of prolonged air leaks. Vricella *et al.* proposed that in patients with advanced AIDS and pneumothorax, if no resolution is observed after simple tube thoracostomy, prompt conversion to a Heimlich valve allows safe and early hospital discharge. In their case series of 59 pneumothoraces in HIV-seropositives with severe immunosuppression (number of CD4+ lymphocytes of less than 100/ μ L), patients treated with a Heimlich valve had 100% pneumothorax resolution versus 72.2% with conventional treatment (tube thoracostomy with or without pleurodesis and thoracotomy with blebectomy) (24).

Surgical approach

As previously mentioned, patients with AIDS-related pneumothoraces tend to have persistent air leaks, related

often with bronchopleural fistula. For this reason sometimes the surgical approach is avoidable. Among surgical interventions, minimally invasive videothoracoscopy seems to be a safe, simple and cost-effective technique and can be used as initial therapy (25). Slabbynck *et al.* reported the diagnostic and therapeutic utility of videothoracoscopy in HIV patients (26). Talc poudrage through the thoracoscopic cannula followed by chest tube drainage was performed in all patients and was successful in treating three of five with proved *Pneumocystis jiroveci* pneumonia-related pneumothorax. Wait *et al.* proposed the use of large-bore intercostal tube drainage, chemical pleurodesis and early video-assisted (thoracoscopic) talc poudrage in an attempt to shorten the duration of hospital stay, hospital costs and mortality (22). Also, Kimmel *et al.* presented a technique of talc insufflation in patients with HIV-associated pneumothorax (27). Even if videothoracoscopy may have a higher reoccurrence index of pneumothorax in comparison with open surgery (28), in many cases could be the procedure of choice, given the poor general status of HIV-infected patients which impedes more invasive therapeutic interventions, even as a last resort. In this case, open lung surgery—traditional thoracotomy with or without pleurectomy—must reserve as an ultimate alternative only for serious problems like marked pleural infection or appearance of bronchopleural fistula (11). Of course the problem in HIV-related pneumothorax is that severe concurrent disease make patients poor operative candidates, so surgical interventions often delay even if seems to be indicated. Nevertheless, even if open lung surgery has an obvious risk, several case series have shown that in properly selected patients has acceptable morbidity and mortality (29-47).

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