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Pleural disease and acquired immune deficiency syndrome

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ABSTRACT: Patients with acquired immune deficiency syndrome (AIDS) do not frequently have pleural complications. However, pneumothorax is a troublesome complication of patients with AIDS. At some medical centres, more than 50% of patients with spontaneous pneumothorax have AIDS. Most patients with spontaneous pneumothorax and AIDS have *Pneumocystis carinii* infection and necrotic subpleural blebs. The pneumothoraces in these patients usually cannot be managed with tube thoracostomy alone. Patients who do not respond to tube thoracostomy are best managed with a Heimlich valve or with thoracostomy with stapling of blebs and pleural abrasion.

Approximately 2% of human immunodeficiency virus (HIV)-positive individuals will have a pleural effusion. Parapneumonic effusions or empyema, tuberculosis and Kaposi's sarcoma are the three leading causes. *P. carinii* infection is frequently responsible for pulmonary infections, but is only occasionally responsible for a pleural effusion. Pleural effusions may also develop from non-Hodgkin's lymphoma (NHL). There is one relatively rare NHL that is associated with the Kaposi's sarcoma associated virus that produces a lymphoma confined to the body cavity.
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The number of patients with acquired immune deficiency syndrome (AIDS) continues to increase and they account for a significant percentage of hospitalizations at least in some communities. Patients who have AIDS frequently have pulmonary complications and these complications at times involve the pleura, producing either a pneumothorax or a pleural effusion. This article reviews current information concerning pneumothorax and pleural effusion which occur in AIDS patients.

Pneumothorax and AIDS

The great majority of patients with AIDS who develop a spontaneous pneumothorax have *Pneumocystis carinii* infection [1, 2]. The risk of spontaneous pneumothorax is also higher if the patient is receiving aerosolized pentamidine, smokes cigarettes or presents pneumatoceles on a chest radiograph [3]. Most patients have CD4+ counts less than 100 cells·μL^{-1} [4]. The incidence of spontaneous pneumothorax was 4% in one series of 408 patients who were receiving prophylactic pentamidine therapy; about 25% of these patient had had *P.*

carinii pneumonia previously [5]. In a more recent study from Bellevue Hospital in New York, the rate of spontaneous pneumothorax was 4.9% in a group of 1,360 patients with AIDS and *P. carinii* pneumonia [6]. At some medical centres where large numbers of patients with AIDS are treated, pneumothoraces in these patients account for a sizeable percentage of all the spontaneous pneumothoraces. At Parkland Memorial Hospital in Dallas, Texas, 27% of all cases of spontaneous pneumothorax between 1983 and 1991 occurred in patients with AIDS [7].

The reason that there is a high incidence of spontaneous pneumothorax in AIDS patients with *P. carinii* infection appears to be the presence of multiple subpleural lung cavities, which are associated with subpleural necrosis [8–11]. Most AIDS patients with *P. carinii* infection and spontaneous pneumothorax will have evidence of fibrocystic parenchymal disease [8]. When the lung is viewed at surgery, there is usually diffuse involvement of the lung parenchyma with greater involvement of the upper lobe. There are usually emphysematous blebs on the surface of the lung and multiple cysts in the apex of the lung [12]. It is common to

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find areas of necrosis in consolidated areas of the lung and these areas are exceedingly friable and prone to laceration with the slightest manipulation. When lung specimens are viewed microscopically, there is usually extensive necrosis with complete loss of the inherent architecture. The reason that patients who are on aerosolized pentamidine are more likely to develop pneumothorax is not definitely known. However, it is hypothesized that aerosolized pentamidine usually does not reach the periphery of the upper lobe. Therefore, a low-grade infection persists and destroys the lung, leading to the development of the cysts and bronchopleural fistulas [13].

It is ominous when a patient with AIDS and *P. carinii* infection develops a spontaneous pneumothorax. In one study, the mean survival time of 22 patients with spontaneous pneumothorax was 147 days after the diagnosis of the pneumothorax [12]. In a second series, the in-hospital mortality was 29% for 35 patients with spontaneous pneumothorax. In a more recent study the in-hospital mortality of 32 patients with *P. carinii* infection and a spontaneous pneumothorax was 50% [14].

Recurrent ipsilateral or contralateral pneumothoraces are very common in patients with AIDS and spontaneous pneumothorax. In one series of 20 patients, ipsilateral recurrences occurred in 13 (65%) and contralateral pneumothoraces also occurred in 13 (65%) [1].

The treatment of the spontaneous pneumothorax in the patient with AIDS is difficult. The difficulty in managing these patients is due to the fact that the visceral pleura is necrotic so that the bronchopleural fistula tends to persist [13]. Conservative therapy consisting of tube thoracostomy with or without a sclerosing agent usually fails. In one reported series 20 patients were treated with a chest tube alone and the treatment was successful in only four despite the chest tube being in place a median of 20 days [1]. In a second series only nine of 35 patients (26%) were successfully managed with a chest tube and tetracycline/doxycycline pleurodesis [15].

Given the poor prognosis of the patient with AIDS and a spontaneous pneumothorax and the poor results with tube thoracostomy with or without sclerosing agents, alternative treatments should be considered. The initial treatment of most patients should be a chest tube. If the air-leak persists after 3 days, then there are basically two choices - a Heimlich valve or operative intervention [13].

The least invasive therapy is to attach a Heimlich valve to the chest tube and send the patient home, not worrying about the closure of the bronchopleural fistula [4]. TRACHIOTIS *et al*. [4] recently reported their experience managing AIDS patients with pneumothorax and reported that they discharged eight of 25 patients with a Heimlich valve. Of the remaining 17 patients, nine died in hospital and nine responded to tube thoracostomy with or without chemical pleurodesis [4]. The advantage of the Heimlich valve is that the patient can be managed as an outpatient, thereby shortening hospitalization [4].

If the patient cannot be managed with a Heimlich valve or if definitive treatment of the pneumothorax is desired, the treatment of choice is probably video thoracoscopy. In one series 11 of 12 patients were successfully managed with video thoracoscopy with the insufflation of 5–10 g of asbestos-free talc without treating the air leaks directly [15]; these authors hesitated to resect the area of the leak because they felt that the necrotic tissue made the resection technically difficult. However, CRAWFORD *et al*. [16] reported the successful management of 13 of 14 patients using thoracotomy with direct closure of the bronchopleural fistula and parietal pleurectomy. Due to the high incidence of contralateral pneumothorax, one group has recommended that patients undergo a median sternotomy incision with bilateral pleurodesis [17]. Video thoracoscopy is preferred over thoracotomy in general because it is associated with less morbidity.

Pleural effusions and AIDS

The reported prevalence of pleural effusion among patients hospitalized with AIDS has varied markedly. The prevalence of pleural effusion was only 1.7% in a very large series of 4,511 HIV positive patients who were admitted to the Metropolitan Hospital Center in New York [18]. In a second series the prevalence of pleural effusion was 18.3% in 350 HIV-positive patients in Charleston, South Carolina [19]. There is no explanation for the markedly different prevalences. In our experience, the prevalence has been closer to 2% than to 20%.

The distribution of the diseases responsible for pleural effusion in patients with AIDS varies widely from series to series. In one series of 61 patients from Paris, 32 (52%) of the patients had Kaposi's sarcoma (KS), 11 (18%) had anaerobic bacterial pneumonia, nine (15%) had tuberculous pleuritis, six (10%) had opportunistic infections, and three (5%) had effusions due to other malignancies [20]. In contrast in a series of 30 patients from New York, 12 (40%) had parapneumonic effusion or empyema, six (20%) had tuberculosis, three (10%) had end-stage renal disease with volume overload, seven (23%) had miscellaneous disease or an unknown aetiology and only two (7%) had Kaposi's sarcoma [18]. The explanation for the differences in the above two studies is in part due to the fact that in the series from Paris most patients were homosexual (KS occurs predominantly in homosexuals) while the series from New York was predominantly intravenous drug users. As might be expected, in Rwanda, tuberculosis was responsible for 82 of 91 (90%) of the effusions in HIV-positive patients [21]. Lastly in a series of 59 patients from South Carolina, the most common cause of pleural effusion was bacterial pneumonia (18 patients (31%)), but hypoalbuminemia was thought to be responsible for the effusion in 11 (19%) and *P. carinii* pneumonia was thought to be responsible for nine (15%) [19]. However, a recent abstract has called into question whether hypoproteinemia itself is a cause of a transudative pleural effusion [22].

Parapneumonic effusion and empyema in patients with AIDS

The incidence of community acquired pneumonia in patients with AIDS has increased. Once a patient with

AIDS develops pneumonia, the pneumonia is more likely to be severe. Parapneumonic effusions are more common in AIDS patients. In one study from Spain [23], the incidence of parapneumonic effusion was 21% (21 out of 99) in HIV-positive patients compared with 13% (116 out of 884) in HIV-negative patients. The incidence of bacteremia was 58% (11 out of 19) in patients with AIDS and parapneumonic effusion compared with 18% (17 out of 96) in patients without AIDS. The parapneumonic effusions were also more likely to be complicated in the HIV-positive individuals [23, 24]. The median pleural fluid glucose levels were lower in the HIV-positive patients [23]. The percentage of patients who required chest tubes were significantly higher in the HIV-positive group (15 out of 21, 71%) than in the HIV-negative group (51 out of 116, 44%). In addition, positive blood or pleural fluid cultures for *Staphyloccoccus aureus* were more common in the HIV-positive group (13 out of 17, 76%) than in the HIV-negative group (17 out of 57, 30%) [23].

The management of patients with AIDS and parapneumonic effusion is similar to the management of the immunocompetent patient with a parapneumonic effusion. Due to the high incidence of infection with *S. aureus*, the patients should be given antibiotics that will cover this organism. Due to their immuno-incompetency, one should probably be more aggressive in placing chest tubes in these patients than in immunocompetent individuals.

Tuberculous pleural effusions in patients with AIDS

As mentioned above, in some series the most common aetiology for pleural effusions in patients with AIDS is tuberculosis [21]. Interestingly, among patients with AIDS, the percentage of tuberculosis cases that have a pleural effusion is higher in patients with CD4+ counts above 200 cells·µL^{-1} than in those with CD4+ counts below 200 cells·µL^{-1} [25]. This observation supports the hypothesis that tuberculosis pleuritis is predominantly due to delayed hypersensitivity rather than a direct infection of the pleural space. Patients who are co-infected with the AIDS virus have some different clinical characteristics than do patients without AIDS. The pleural fluid acid-fast bacillus (AFB) stain is positive in ~15% of patients with AIDS [26] but in only ~1% of patients without AIDS [13]. The pleural fluid and the sputum culture are each positive in 40–50% of patients with AIDS but in only 10–15% of patients without AIDS [27]. In patients with tuberculous pleuritis, the purified protein derivative (PPD) skin test is less likely to be positive if the patient has AIDS [26, 27].

Patients with AIDS also have significantly different findings in their pleural fluid. Measurement of the pleural fluid adenosine deaminase (ADA) levels appear to be less sensitive in identifying patients with tuberculosis in AIDS patients than in non-AIDS patients [28]. Also, levels of tumour necrosis factor alpha are significantly lower in patients with AIDS than in patients without AIDS [29]. However, the levels of interferon-gamma in the pleural fluid are raised by the same amount in patients with AIDS and pleural tuberculosis as they are in other patients with pleural tuberculosis [30].

The diagnosis of tuberculous pleuritis in HIV-infected patients is made in the same way as it is in patients who are not HIV-infected. The diagnosis is established by demonstrating AFB in the pleural fluid, sputum or pleural biopsy material or by culturing *Mycobacterium tuberculosis* from the sputum, pleural fluid or pleural biopsy specimen. The diagnosis can also be made by demonstrating granulomas in the pleural biopsy specimen. As mentioned above, pleural fluid ADA levels are less useful in making the diagnosis of tuberculous pleuritis in HIV-infected individuals.

The treatment of tuberculous pleuritis in HIV-infected patients is essentially the same as that for any patient with tuberculous pleuritis. The initial phase of a 6 month regimen should consist of a 2 month period of isoniazid (INH), rifampin, and pyrazinamide. Ethambutol should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance. The second phase of the treatment should be isoniazid and rifampin given for 4 months. However, if there is evidence of a slow or sub-optimal response, therapy should be prolonged and judged on a case by case basis [31].

Pleural effusions due to Kaposi's sarcoma (KS)

KS is one of the most common causes of pleura effusion in patients with AIDS. Recently it has been demonstrated that deoxyribonucleic acid (DNA) sequences of the human herpes virus 8 (HHV8) can be regularly isolated from KS material and it has been hypothesized that this virus has a pathogenetic role in KS [32]. This virus is also called KS-associated virus (KSHV). The KSHV has also been propagated from KS lesions [33].

KS occurs almost exclusively in homosexual patients with AIDS and the prevalence of KS is 20–25% in these patients [34, 35]. The most common presentation of KS is as cutaneous violaceus plaques. Pleuropulmonary KS occurs in ~20% of patients with cutaneous KS [35]. The chest radiograph of patients with pulmonary KS generally shows bilateral infiltrates [35]. Approximately 50% of patients with pulmonary KS have pleural effusions and most of them will have bilateral parenchymal infiltrates [35]. The pleural effusions may be unilateral or bilateral. The computed tomography (CT) scan of patients with pulmonary KS usually reveals numerous nodules, tumoural masses and bronchovascular pathways thickening [36]. In one series of 53 patients, 29 (55%) had pleural effusions which were bilateral in 76% [36]. At autopsy, patients with pulmonary KS have multiple cherry red to purple lesions on the visceral but not on the parietal pleural surface [35].

The pathogenesis of the effusion with KS is unknown. The pathogenesis of most effusions due to malignancy has been attributed to blockade of the lymphatic drainage system which is located in the parietal pleura. We have questioned this assertion in a recent editorial [37], and feel it is particularly unlikely in patients with KS pleural effusions, since their parietal pleura is not involved. In patients with KS the pleural effusion is a chylothorax in ~20% which suggests involvement of the thoracic duct by the tumour in these cases. In the remainder of the patients with KS and pleural effusion,

we hypothesize that the effusion is due to the elaboration of vascular endothelial growth factor (VEGF). VEGF is elaborated by many tumours and promotes microvascular hyperpermeability so that extravascular fluid is formed [38]. VEGF is present in large quantities in AIDS-KS cell-derived conditioned media [39]. It is, therefore, quite possible that VEGF could be responsible for the pleural effusion. In addition, many of the effusions are bloody and this could also be explained by VEGF since VEGF is also angiogenic [38].

The definitive diagnosis of pleural KS is not easy. The pleural fluid is an exudate that is usually serosanguineous or haemorrhagic. The diagnosis cannot be established with cytology because the diagnosis requires a characteristic architectural appearance and not a particular neoplastic cell type [34]. The diagnosis cannot be made with needle biopsy of the pleura because the parietal pleural is not involved. The diagnosis can be established by thoracoscopy with the characteristic appearance of the KS lesions on the visceral pleura [35]. One report several years ago suggested that the diagnosis could be made by immunocytochemical staining of the cells in the pleural fluid with CD34 antibody, a newly recognized marker for vascular neoplasia [40]. However, since there have been no confirmatory reports since the original one, its validity must be questioned. In most cases a presumptive diagnosis is based on the clinical picture and the characteristic bronchoscopic picture [41].

The treatment of the pleural effusion secondary to KS is difficult. Tube thoracostomy with the instillation of tetracycline is usually not successful. Insufflated talc is probably the treatment of choice if the diagnosis is made with thoracoscopy. Otherwise, pleurodesis *via* talc in a slurry or a pleuroperitoneal shunt are probably the best alternatives.

Pleural effusion due to lymphomas

Malignant lymphomas represent the second most common neoplasm associated with HIV infection [42]. Most AIDS-related lymphomas are B-cell non-Hodgkin's lymphoma (NHL) and most can be classified as Burkitt-like (40%), large cell (30%) and large cell immunoblastic (30%) lymphoma [42]. The incidence of NHL in HIV-infected individuals is estimated to be 60–100 times higher than expected [42]. A less common type of NHL is the KSHV related lymphoma. This uncommon lymphoma grows mainly in the body cavities and presents as a lymphocyte predominant effusion without an identifiable contiguous tumour mass [43]. The consistent presence of KSHV and certain other features suggest that this is a distinct entity. In one series [44], KSHV was sought in lymphomas from 42 patients with AIDS. All eight of the body-cavity-based lymphomas were associated with KSHV while none of the other 34 lymphomas were [44].

In a recent article NADOR *et al.* [43] studied 19 malignant lymphocyte-predominant pleural effusions occurring in the absence of a contiguous tumour mass for their clinical, morphological, immunophenotypic, viral, and molecular characteristics. They found that KSHV was present in 15 of the 19 lymphomas. All four KSHV

negative lymphomatous effusions exhibited Burkitt or Burkitt-like morphology and c-myc gene rearrangements and therefore appeared to be Burkitt-type lymphomas. In contrast the KSHV-positive lymphomas exhibited a distinctive morphology bridging large-cell immunoblastic lymphoma and anaplastic large-cell lymphoma and all lacked the c-myc gene rearrangements. Of the KSHV-positive lymphomas, all occurred in men, 13 out of 15 in association with HIV infection, in all of which homosexuality was a risk factor. Of these 15 cases, 14 presented as a lymphocyte-predominant effusion and 13 remained localized to the body cavity of origin.

At times pleural effusions are seen in conjunction with NHL which is unrelated to KSHV. Between 6 and 30% of patients with NHL and AIDS will have intrathoracic involvement [45]. EISNER *et al* [46] reviewed the clinical characteristics of 38 patients with HIV infection, NHL, and pulmonary involvement. Thoracic CT revealed pleural effusions in 26. The pleural effusion was bilateral in 23 and unilateral in 15. Other radiographic abnormalities in the 38 patients included lobar consolidation in 15, pulmonary nodules in 15, reticular infiltrates in nine and mass in nine. Certainly some of these 38 patients had KSHV associated lymphoma, but the majority did not.

The pleural fluid in these patients is an exudate and is characterized by a very high lactic acid dehydrogenase (LDH) level. In one series, the mean LDH was 2,535 IU·L^{-1} and the ratio of pleural to serum LDH was 3.12 [46]. The diagnosis can usually be established with pleural fluid cytology [46].

The prognosis of patients with AIDS-associated lymphoma is poor, with a median survival of 4–6 months [44]. It is still unknown whether it is better to treat these patients aggressively or conservatively. The aggressiveness of the tumour suggests that intensive therapy would be advantageous, but there has been a high frequency of death from infections in those treated intensively [44].

Pleura effusions due to P. carinii *pneumonia*

Although *P. carinii* is a frequent cause of pulmonary infiltrates in the patient with AIDS, it is an unusual cause of pleural effusion. Only seven cases of pleural effusion due to *P. carinii* had been reported up until 1993 [47, 48]. All seven of these patients were receiving aerosolized pentamidine, and five of the seven had documented *P. carinii* pneumonia [13]. It appears the Pneumocystis pleural disease is an extension of smouldering subpleural *P. carinii* pneumonia and the prognosis is similar to that for patients with pneumonia alone [13]. A bronchopleural fistula was present in four of the seven patients with *P. carinii* pleural effusion [47].

The pleural fluid of patients with Pneumocystis pleural effusion has an LDH which exceeds the upper limit of normal for serum and the pleural fluid to serum LDH ratio has exceeded 1.0. However, the pleural fluid protein level has been below 3.0 gm·dL^{-1} in all patients. The differential cell count can reveal either neutrophils or mononuclear cells and the pleural fluid glucose and pH are not reduced [47]. The presence of the pleural effusion does not alter the drug treatment of pulmonary

Pneumocystis infection. However, if a bronchopleural fistula is present, a chest tube should be inserted.

Miscellaneous cause of pleural effusions

On occasion other opportunistic diseases such as cryptococcosis [49], nocardiosis [50], histoplasmosis [51], aspergillosis [52], or atypical mycobacteria [53] are responsible for an exudative pleural effusion in the patient with AIDS. In addition, systemic problems such as left ventricular failure or renal failure may cause transudative pleural effusions.

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