

Pulmonary Fungal Involvement in HIV-positive patients in an inner city hospital in New York

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Abstract

Study objective: Pulmonary fungal infections are being recognized with increasing frequency in AIDS patients. The goal of our study was to determine the incidence at autopsy of fungal and non-fungal pneumonia in HIV patients, compare these two groups and evaluate possible risk factors for fungal infection.

Patients: This was a retrospective review of all HIV positive patients that died and had autopsy performed between January 1993 and June 1996.

Results: There were 5,925 pneumonia events reported by discharge billing codes in 2903 HIV positive adult patients at the Bronx-Lebanon Hospital Center in New York City from 1993 to 1996. During the 42 month study period, 688 (24%) of the patients died. Ninety (13%) patients underwent autopsy at our institution; 70 (77%) of those patients were found to have pneumonia at autopsy.

Fungal pneumonia was present in 29 (41%) patients: *Candida* (14), *Aspergillus* (8), *Histoplasma* (4) and *Cryptococcus* (3). Three patients were being treated for fungal infection premortem, 2 *Cryptococcus meningitis* and 1 disseminated histoplasmosis. In the 41 cases with non-fungal pneumonia, bacterial infections, *Pneumocystis jirovecii* and CMV were most frequently found organisms. Neutropenia was seen in 41% of the patients with fungal pneumonia compared with 15% in the non-fungal pneumonia group. This was a statistically significant difference ($p=0.05$). Neutropenia was associated most commonly with pulmonary candidiasis. Cavitory lung disease was found only in patients with Aspergillosis and tuberculosis. Infection with multiple organisms was frequently found.

Conclusion: Pulmonary fungal infections in AIDS patients are a common and under diagnosed problem. Neutropenia is an important risk factor for pulmonary candidiasis. Our study highlights the need for a high index of clinical suspicion and early aggressive diagnostic intervention in AIDS patients with neutropenia and pneumonia, especially in those patients with cavitory or alveolar patterns on CXR.

ABBREVIATIONS

HIV=human immunodeficiency virus

LDH=lactate dehydrogenase

PCP= *Pneumocystis jirovecii*

FFB=Flexible fiberoptic bronchoscopy

CMV= Cytomegalovirus

TBBx=Transbronchial biopsy

AIDS= acquired immunodeficiency syndrome.

CXR=Chest roentgenograms

INTRODUCTION

HIV infection is the leading cause of death among adults 25 to 44 years of age in many urban communities. While it is

difficult to define the impact of the human immunodeficiency virus (HIV) pandemic on the field of fungal infections, an increase in the number and severity of serious fungal infections has been reported. Fungal disease at any anatomic site accounted for over 20% of the AIDS-defining diseases reported to the Centers for Disease Control (CDC) between 1987 and 1988. Because most pulmonary fungal diseases have not been considered as AIDS defining, this 20% could be an underestimation of their incidence. Necropsy studies in AIDS patients have showed a incidence of fungal infection of 20% to 49%.^{1,2}

Two decades of the HIV epidemic in America have seen

significant shifts in patient demographics, with increasing percentages of women, Hispanic and blacks being affected.

HIV-related mortality continues to be a significant problem in the United States and other countries. Causes of mortality are best determined by autopsy, and studies of many patient populations have demonstrated the utility of postmortem analysis. ^{3,74}

The goal of our study was to determine the incidence of pulmonary mycosis in HIV infected patients at autopsy, identify possible risk factors for fungal infection in our population and compare those patients with pulmonary fungal infection to those without it.

METHODS

This was a retrospective review of the medical records and autopsy results of all HIV infected patients that died at Bronx Lebanon Hospital between January 1993 to June 1996 and had a complete autopsy done. Data regarding demographics, microbiology and laboratory studies, CD4 cell count, white blood cell count with the absolute neutrophils counts, antibiotics and steroids use was analyzed. Results of all pulmonary diagnostic procedures were reviewed, i.e. flexible fiberoptic bronchoscopies (FFB), open lung biopsies. Chest roentgenograms (CXR) were reviewed by two of the authors (ES, CS).

AIDS was defined according to the CDC definition. Neutropenia was defined as an absolute neutrophils count <1,000/mm³ at least once during the hospital stay. Corticosteroid use was defined as the use of the equivalent of 20 mg or more of prednisone daily for at least 10 days. Antibiotic treatment was considered a risk factor when prescribed for 10 days or more.

A patient was considered to have invasive pulmonary mycosis if pathological examination of the lung tissue either antemortem or postmortem showed evidence of vascular and/or parenchymal invasion by hyphae or yeast elements. Identification of the fungus was made by histology and/ or cultures. Routine stains used in the department of pathology were hematoxylin & eosin stain, Gomori ammonium silver stain, mucicarmine stain and acid-fast stain.

The chi square test was used for statistical analysis. A p value of ≤ 0.05 was considered significant.

RESULTS

There were 5,925 pneumonia events reported by discharge billing codes in 2903 HIV positive adult AIDS patients at

the Bronx-Lebanon Hospital Center in New York City from 1993 to 1996. The Center is a 725-bed, acute-care facility in the south Bronx, which serves a population of approximately half a million people. During the 42 month study period, 688 (24%) of the patients died. Ninety (13%) patients underwent autopsy at our institution; 70 (77%) of those patients were found to have pneumonia at autopsy. In 29 of those patients, a fungus was identified in the lung tissue. High poverty levels, tuberculosis and AIDS incidence, and intravenous drug abuse are common in this population. Subjects were predominantly Hispanic and African American.

There was no difference in demographic characteristic as well as degree of immunosuppression between patients with and without fungal pneumonia Table 1 and 2.

Figure 1

Table 1: Demographic and data characteristic

Variable	Fungal pneumonia positive N=29 (%)	Non-Fungal pneumonia N=41 (%)	P value
Age (mean)	39	42	NS
Sex (male)	20 (69%)	28 (68%)	NS
Ethnicity			
Hispanic	13 (45%)	21 (51%)	NS
African-American	13 (45%)	19 (46%)	
Other	3 (10%)	1 (3%)	
Neutropenia	12 (41%)	6 (15%)	p= 0.05
Antibiotics use	20 (69%)	19 (46%)	p=0.32
Steroids use	7 (24%)	6 (15%)	p= 0.41

Figure 2

Table 2: Etiology of Pulmonary Mycosis and CD4 cells counts.

Fungal Pneumonia	N=29	CD4 count (range)
Candida	14 (48%)	99 (1-288)
Aspergillus	8 (28%)	19 (1-106)
Histoplasma	4 (14%)	44 (1-106)
Cryptococcus	3 (10%)	48 (1-94)
Non Fungal Pneumonia	41	56 (0-352)

There was no history of traveling to an endemic area for fungal infections. The most common isolated fungus in lung tissue was Candida (albicans 12, glabrata 2) followed by Aspergillus (fumigatus 6, flavus 2), Histoplasma capsulatum and Cryptococcus neoformans Table 2. A pre-mortem diagnosis of mycosis was available in only three of the 29

(10%) patients with fungal pulmonary involvement; two had Cryptococcus meningitis and one disseminated histoplasmosis with positive peripheral smears.

Three patients were being treated for PCP at the time of demise, one was found to have Candida albicans and two Aspergillus fumigatus in autopsy.

FFB was performed in five out of the 70 patients with pneumonia; bronchoalveolar lavage (BAL) in 2 and BAL plus biopsy in three. No fungus was identified in any of them. All five of these patients had pulmonary Aspergillosis on autopsy. There were 41 patients that had a non-fungal pneumonia. An etiology for the pneumonia was found in 24 (59%). In 14/24 (58%) patients, the etiology of the pneumonic process was identified only by necropsy. Concomitant involvement by Pneumocystis jirovecii and Cytomegalovirus was seen in five patients, the diagnosis made only at postmortem. Table 3

Figure 3

Table 3: Etiology and source of isolated pathogen in non fungal pneumonia

Pathogens	Pre and post mortem	Postmortem only N=14	Total Diagnosis N=24
PCP	5	3	5
PCP plus CMV	0	5	5
CMV	0	1	1
Mycobacterium tuberculosis	0	1	1
Mycobacterium Avium Intracellulare	0	1	1
Staphylococcus aureus	5	2	5
Gram negative bacilli	4	1	4
Streptococcus pneumonia	2		2

Co-morbid conditions present in our patients were chronic renal failure (6), malignancy (5), disseminated Mycobacterium Avium Intracellulare (MAI) (2), Cytomegalovirus (CMV) ventriculitis (1). The malignancies were Kaposi Sarcoma (3), lymphoma (1) and cancer of the tongue (1).

Review of laboratory data and use of antibiotics and steroids showed that neutropenia was statistically more common in patients with fungal than non fungal pneumonia Table 1. Nine of the 12 patients with neutropenia in the fungal group had Candida pneumonia. There were no differences between the two groups for serum LDH, use of antibiotics or corticosteroids or length of hospital stay.

Chest roentgenograms (CXR) were available for review in 63 (90%) of the patients, 29 and 34 in the fungal and non-fungal group respectively Table 4.

Figure 4

Table 4: Radiologic findings in patients with and without fungal pneumonia.

Radiologic Findings	Candida n=14	Aspergillus n=8	Histoplasma n=4	Cryptococcus n=3	Non Fungal n=34	Total N=63
Cavitary	0	4	0	0	1	5
Focal Alveolar	8	1	1	1	8	19
Bilateral Alveolar	4	3	3	2	6	18
Bilateral Interstitial	0	0	0	0	12	12
Normal	2	0	0	0	7	9

Majority of patients with fungal pneumonia had abnormal CXR when compared with patients with non fungal pneumonia, 93% versus 79% respectively. Out of the seven patients with non fungal pneumonia and normal CXR, autopsy revealed CMV in two and PCP in two patients. No pathogen was identified in the remaining three patients with normal CXR, despite pathological changes consistent with pneumonic process.

Cavitary disease with thick wall cavities was seen in five (8%) of the 63 patients with CXR available for review. Four of them had Aspergillosis and another, pulmonary tuberculosis.

Interstitial infiltrates was seen only in patients with non fungal pneumonias. In 8 of these 12 patients either PCP, CMV pneumonia or both was identified.

DISCUSSION

The incidence of fungal pneumonia in our study group was 41%. The reported incidence ranges from 14 to 53%.^{1,2,3} In an autopsy series performed in patients with AIDS, fungal infections with lung involvement has been reported frequently. Candida, followed by Cryptococcus and Aspergillus are the most common organism isolated.^{2,3,4} In those series, more than 50% of the diagnoses considered to be of important clinical significance had not been suspected antemortem.

Our findings support the data of other researchers regarding the high incidence of pulmonary candidiasis, Candida was the most common fungus isolated in lung tissue in our series, being present in 48% of cases. Several studies report an incidence of 45 to 60%.^{2,3,5} Autopsy reports of patients with

pulmonary candidiasis failed to reveal any clinical predictors for this diagnosis ⁶

Invasive pulmonary aspergillosis is seen most often in patients who have marked immunosuppression such as hematological malignancies or neutropenia, and those receiving corticosteroid or cytotoxic agents. Remarkably, aspergillosis is unusual in patients with AIDS and is not included as an AIDS-defining condition by the Centers for Disease Control (CDC) criteria.⁷ The incidence of Aspergillosis in necropsy series ranges from less than 1% to 7% in the AIDS population and is commonly associated with neutropenia.^{3,7} The clinical diagnosis of pulmonary Aspergillosis is difficult and elusive even when FFB is performed and most of the data available in AIDS patients come from autopsy studies. The true incidence of Aspergillus infection among HIV infected patients is difficult to estimate. A survey of autopsy series demonstrated a prevalence of 4%.^{8,9} In the report of Niedt et al. 22% of their patients with fungal pneumonia had Aspergillus very similar to the 28% in our study. ²

Histoplasmosis occurs in less than 1% of patients from areas of non-endemicity, where reactivation of latent infection is more likely than exogenous infection.

Exposure to microfoci of fungi containing *H. capsulatum* as risk for exogenous infection has been reported in AIDS patients with low CD4 cell counts. Two of the patients in our group that had histoplasmosis were Hispanic.

Radiographic findings often resemble those seen in patients with *Pneumocystis jirovecii* pneumonia, emphasizing the need to perform invasive studies to establish the correct diagnosis so that appropriate treatment may be given. Concurrent infection with PCP may occur in up to 25% of cases ¹⁰

A number of factors may be associated with the increasing incidence of pulmonary fungal infection reported in the literature. Impaired T-lymphocyte function due to

high-dose steroid therapy, chemotherapy, or AIDS, as well as depressed neutrophil count or function due to hematologic malignancies, or chemotherapy, may increase the risk of fungal infection. The increase use of invasive devices, broad-spectrum antibiotics and hyperalimentation may also contribute to the development of fungal infection.

Previous clinical studies have shown that the radiographic manifestations of invasive pulmonary fungal infections in

AIDS patients are heterogeneous; the most common abnormalities include cavitory lesions in 29 to 42% and bilateral interstitial or alveolar infiltrates in 23 to 55% of patients.^{11,12,16,17} Our findings are consistent with those reports, we did not find any specific radiological feature that could favor one specific fungus versus other.

In those patients with non- fungal pneumonia, PCP was a common etiology for the pulmonary pathology, found in 10 of the 15 patients (67%) who had an organism identified. Our data is consistent with other necropsy series, Niedt et al. reported 35 of 56 (63%) patient with CMV pneumonia and Hui et al found PCP in 8 of 12 (66%) patients; PCP was a postmortem finding in 7 patients.^{2,13}

Consistent with a prior report from our institution, we note the presence of infections by multiple organisms, ie fungal and PCP. ¹⁴ Awareness of these changing patterns of infection may be useful in treating persons with AIDS

There was a paucity of invasive diagnostic pulmonary procedures done in our study patients and this was probably due to a combination of factors. The most important was the severity of illness of this population, with many patients having coagulation abnormalities that precluded the performance of invasive procedures. In addition, advance directives or family wishes limited the care to supportive measures in many of our patients.

Neutropenia was the only statistically significant difference found between patients with and without pulmonary mycosis. Unlike the other reports, neutropenia was more common in patients with disseminated candidiasis (9 patients) than Aspergillosis (3 patients). Neutropenia have been reported in up to 50% of patients with AIDS and Aspergillosis ^{12,15}.

In summary, pulmonary fungal infections in AIDS patients are a common and unrecognized problem. Owing to the difficulty of diagnosis of clinically unsuspected fungal disease and the nonspecific laboratory and radiographic findings, the diagnosis is frequently not made until autopsy. In the presence of a severely immunosuppressed HIV infected patient, the findings of neutropenia, unexplained bilateral alveolar infiltrates or cavitory lesions on CXR should alert the clinician to the possibility of a fungal infection. The main problem in dealing with pulmonary fungal infection is in distinguishing simple colonization from invasive or disseminated infection. Cultures of respiratory specimens obtained at

bronchoscopy can be falsely negative in up to 50% cases so the decision to consider more invasive diagnostic procedures including transbronchial biopsy and open lung biopsy versus empiric antifungal treatment should be made early in the clinical course. The clinical outcome of AIDS patients with pulmonary or disseminated fungal infection is dismal even when specific treatment is attempted, however, a more invasive approach might have identified those patients with PCP, CMV or tuberculosis, where response to treatment is more favorable.

The diagnosis of disseminated fungal infections requires a high index of clinical suspicion and awareness of the uses and limitations of the tests commonly used to identify fungal diseases.

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