Short Communication

Journal of Iranian Medical Council, Volume 6, Issue no. 1
http://dx.doi.org/10.18502/jimc.v6i1.11855

Etiology and Contributing Factors of Cavitary Pulmonary Lesions in HIV Infected Patients

Mitra Rezaei[1,2], Faraz Mohamadi[2], Makan Sadr[3], Mojdeh Azimi[2], Afshin Moniri[2], Mehdi Kazempour Dizaji[4], Payam Tabarsi[2], Majid Marjani[2]* and Ali Akbar Velayati[4]

1. Department of Pathology, School of Medicine, Shahid Beheshti University of Medical Sciences,Tehran, Iran
2. Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Virology Research Center, National Research Institute of Tuberculosis and Lung Disease, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

*** Corresponding author**
Majid Marjani, MD
Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel/Fax: +98 21 2610 9590
Email: Marjani@sbmu.ac.ir

Received: Jan 31 2022
Accepted: Jun 22 2022

Citation to this article:
Rezaei M, Mohamadi F, Sadr M, Azimi M, Moniri A, Kazempour Dizaji M, et al. Etiology and Contributing Factors of Cavitary Pulmonary Lesions in HIV Infected Patients. *J Iran Med Counc. 2023;6(1):167-73.*

Abstract

Background: This study aimed to investigate the etiology and contributing factors of cavitary pulmonary lesions in HIV infected patients.

Methods: In this study, 844 HIV infected patients with a total of 1000 admissions were investigated at Masih Daneshvari Hospital from Aug 2010 to Oct 2019. After excluding the missing data and distorted documentation, 746 cases and 878 admission episodes finally underwent statistical analysis. The CXRs were observed thoroughly and the cavitary lesions were identified. Eventually, demographic data, diagnostic information, and laboratory findings were extracted and analyzed.

Results: Of the 878 episodes of hospitalization, cavitary pulmonary lesions were observed in 145 documents. The most prevalent etiology was TB with 105 cases (72.5%). After that, *Pneumocystis jiroveci* and septic embolism were responsible for a further 7.6% and 5.6% of the total lung cavities, respectively. 58.5% of the cavities were present in a single lobe, with men being affected in 90.2% of the cases. The upper lobes were the most common site of involvement in the lungs [42.9% for Left Upper Lobe (LUL) and 52.3% for Right Upper Lobe (RUL)]. The rate of definitive diagnosis was significantly higher in patients affected with cavitary lesions (82.8%) in comparison with the unaffected (74.8%) (p=0.001). No significant difference in demographics, HIV and ART status, $CD4^+$ cell count, viral load, and mortality was evident between the two groups.

Conclusion: The most common etiology of cavitary lesions in HIV positive patients was attributable to TB, PJP, and septic embolism respectively. Cavitary lesions were more prevalent in males and mainly tend to involve the upper zones of pulmonary parenchyma.

Keywords: AIDS, Cavitary lesions, HIV infection, Respiratory infections, Tuberculosis

Introduction

HIV and AIDS remain among the most overwhelming health concerns globally, undermining humans' physical and mental well-being. The WHO demonstrates that the total number of HIV infected individuals in 2019 was about 38 million persons, of which 1.7 million were reported to be new-onset cases. Moreover, the mortality of HIV in the same year was estimated to be about 690000 persons due to direct or indirect complications of the virus (1). When it comes to Iran, authorities announce mean rates of 59 thousand affected patients (33-130 thousand), 4100 new-onset cases (1200-12000), and about 2500 deaths (1200-5600). The two cardinal dissemination routes were reported to be intravenous drug abuse and sexual transmission with HIV prevalence of 9.3% and 2.1% in each group, respectively (2). A pulmonary cavity is a gas-filled area of the lung in the center of a nodule or area of consolidation and maybe clinically observed by the use of plain chest radiography or computed tomography. Cavities are present in a wide variety of infectious and noninfectious processes (3). Differential diagnoses for pulmonary cavity in immune-competent population include primary and secondary malignancies, bacterial, fungal, and mycobacterial infections as well as collagen vascular disorders such as Wegener Granulomatosis (4). However, in HIV immune-compromised population infectious causes and malignancies are the most prevalent issues (4). From the beginning of the HIV outbreak, pulmonary super-infections were among its foremost prevalent complications; however, other non-infectious etiologies, such as primary lung cancers, metastatic lesions, pulmonary hypertension, and bronchiectasis have been observed in this population as well (5). Almost 70 percent of HIV positives would experience at least one serious pulmonary complication during the disease, which in most cases is owing to an infectious origin (5,6). For instance, lower respiratory tract infections are 25 times more prevalent in HIV patients (7). In a study from Iran, pulmonary tuberculosis was the most frequent (64.8%) and *Pneumocystis jiroveci* (*P. jiroveci*) was the second infectious agent (13.2%) of lung infections among HIV cases. Bronchiectasis and chronic obstructive pulmonary disease exacerbation were on the top of the list of non-infectious causes, 32.8%, and 28.1%, respectively (8).

Early diagnosis of pulmonary cavity lesions and other complications is pivotal in improving patients' prognoses (9). Thus, studies that describe regional etiologies would surely help physicians to have a better approach to HIV patients who are suffering from pulmonary complications.

The present study aimed to investigate the etiology and contributing factors of cavitary pulmonary lesions in HIV infected patients.

Materials and Methods

The present study was devised retrospectively. As a result, all data were collected from medical records of patients admitted to Masih Daneshvari Hospital from Aug 2010 to Oct 2019. All the adult patients (over 18), who were admitted secondary to HIV pulmonary complications during the mentioned period, were enrolled in the study. Radiographic documentations were extracted either by archived radiologic reports or Picture Archiving and Communication System (PACS), to identify those who were suffering from cavitary lesions. Other relevant data were extracted from Hospital Information System (HIS). In addition, cases with distorted documentaries or unavailable radiographic data were excluded from the study. The variables specifically consisted of demographic information along with probable means of HIV infection and CD4 cell count.

The study was approved by the Research Medical Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval number: IR.SBMU.NRITLD.REC.1398.036).

Statistical analysis

All data underwent statistical analysis using SPSS software (version 16). The frequency of demographic information was shown with descriptive studies. Proportions and averages and standard deviations described quantitative and numeric variables. Qualitative variables were compared between groups with the Chi-square test.

Definitions of confirmed cases

Community-acquired pneumonia: Clinical presentation and accompanying radiographic features suggestive of pneumonia, after rule out of TB or

concurrent positive blood culture or BAL (Broncoalveolar Lavage) culture with colony count over 10^4 *CFU/ml*.

Pulmonary TB: Pulmonary tuberculosis was identified with positive mycobacterial culture or Polymerase Chain Reaction (PCR) test. For those cases whose specimens had undergone histopathologic evaluation, diagnosis of TB was confirmed by granuloma identification, provided that other probable etiologies were excluded.

Non-Tuberculous Mycobacteria (NTM): were defined according to the latest protocol offered by the American Thoracic Society (ATS) (10).

Pneumocystis Jiroveci (PJP): P. jiroveci was confirmed with special staining or immunohistochemistry assays in BAL or a biopsied specimen.

Pulmonary aspergillosis: The definitive diagnosis was based upon either direct observation of invasive fungal elements in tissue or BAL galactomannan equivalent or greater than one.

Results

In general, 844 patients were selected, who had been infected with HIV and were admitted to our hospital from Aug 2010 to Oct 2019. Among these cases, 746 patients were admitted due to respiratory issues, of which a sizable minority was admitted several times due to miscellaneous complications. Eventually, 1000 episodes of admission secondary to respiratory problems were spotted and 4 cases were excluded because they were under 18 years old. The final total number of 996 episodes of admission was then submitted (Table 1).

Following a careful investigation, it turned out that partial distortions were present in the records and imaging of 118 out of 996 admissions. Thus, incomplete records were excluded and a final of 878 episodes was enrolled in the study, undergoing investigations about cavitary lesions. Table 2 provides a complete scope of patients' demographics as well as their general information on HIV condition, disease severity regarding CD4 count, and previous antiretroviral therapy administration.

After detailed pulmonary radiologic observation, it turned out that 145 cases were presented with cavity formation. The cardinal etiology for cavity formation in these 145 cases was demonstrated to be pulmonary

Table 1. General data of 746 HIV affected patients with secondary respiratory complications

Parameter	N (%)
Age (years)	
(Mean ± SD)	38.7±9.5
Sex	
Male	673 (90.2%)
Female	73 (9.8%)
Risk factors for HIV infection *	
IDU	501 (67.2%)
Sexual contact	59 (7.9%)
Prison	377 (50.5%)
Tattooing	132 (17.7%)
Others	30 (4%)
Unknown	130 (17.4%)

* Many patients had more than one risk factor for HIV infection.
SD: Standard Deviation, HIV: Human Immunodeficiency Virus, IDU: Intravenous Drug User.

Table 2. General information of 878 admission episodes with available medical records

Parameter	N (%)
Age (years)	
Mean ± SD	38.5±9.4
Range	18-83 years
Gender	
Male	798 (90.9%)
Female	80 (9.1%)
$CD4^+$ cell count[1] (*cells/mm*^{3})	
Mean ± SD	101±152
Median	45
Range	1-1445
HIV diagnosis[2]	
New cases	297 (33.8%)
Known cases	564 (64.2%)
ART situation	
Drug naïve	510 (58.1%)
Under ART	222 (25.3%)
Interrupted treatment	104 (11.8%)

* Many cases had more than one risk factor for HIV infection. 1) CD4 cell count was available in 700 episodes. 2) Missing data: 17.
SD: Standard Deviation, HIV: Human Immunodeficiency Virus, ART: Antiretroviral Therapy.

Tuberculosis, responsible for 105 admissions (72.5%). The second most identified culprit turned out to be PJP, affecting 7.6% of all cases. A further 5.6% were affected by septic emboli as the third common etiology. Of the total 11 patients diagnosed with PJP, 6 patients were concomitantly infected with active tuberculosis. No other diagnosis was found except for PJP, which was diagnosed definitely in two cases and was the most probable diagnosis in the remaining three cases.

Of those affected by Pneumonia, in 4 out of 5 cases the contributing microorganism was identified: two cases with *Pseudomonas*, one *Staphylococcus aureus (S. aureus),* and one *Acinetobacter* infection. In the fifth case despite Bronchoscopy as well as bronchial lavage the responsible germ could not be identified. Therefore, concerning acute presentation as well as appropriate antibiotic treatment response, the impression was recorded as pneumonia. After all, in 14 cases (9.6%) the etiology of the lesion could not be identified despite all diagnostic measures (Table 3).

Radiologic images were analyzed concerning the site of infection. The dominant pattern of lung involvement was determined to be single lobe and most often occurring among upper zones (Table 4).

Table 3. Etiology of cavitary lung lesions

Diagnosis	N (%)	Comments
Tuberculosis	105 (72.4%)	
PJP	11 (7.6%)	6 concurrent active TB
Septic emboli	8 (5.6%)	1 concurrent PE
CAP	5 (3.4%)	For etiology see text
Actinomycosis	2 (1.4%)	
Nocardiosis	2 (1.4%)	
Bronchiectasis	1 (0.7%)	
Lung abscess	1 (0.7%)	
NTM	1 (0.7%)	M. simiaei
Aspergillosis	1 (0.7%)	
Lymphoma	1 (0.7%)	
Unknown	14 (9.6%)	

PJP: Pneumocystis Jiroveci Pneumonia, TB: Tuberculosis, PE: Pulmonary Embolism, CAP: Community-Acquired Pneumonia, NTM: Non-Tuberculosis Mycobacteria

Table 4. Lung involvement pattern of cavitary lesions

Location	N (%)
Single lobe	75 (58.5%)
Multilobar	43 (33.5%)
Diffuse[1]	10 (7.8%)
LUL	55 (42.9%)
Lingula	2 (1.5%)
LLL	20 (15.6%)
RUL	67 (52.3%)
RML	8 (6.2%)
RLL	17 (13.2%)

1. Diffuse: disseminated involvement of the lungs
Missing data: 17
LUL: Left Upper lobe, LLL: Left lower lobe, RUL: Right Upper Lobe, RML: Right Middle Lobe, RLL: Right Lower Lobe

Lastly, two groups were proposed: HIV infected patients with lung involvement and cavity (145 patients) and HIV patients with lung involvement without cavity (733 patients). Cavitary lesions were significantly more prevalent in male patients (97.9 *vs.* 89.5%). Furthermore, a definitive diagnosis was made more abundantly in patients with cavitary lesions (82.8 in comparison with 74.8%). ESR levels were reported to be 83±37 *mm/hr* in patients with cavitary involvement, whereas this number in the group without cavity was 74±38 *mm/hr*. Age, HIV status, ART status, $CD4^+$ lymphocyte cell count, viral load, and mortality did not show significant disparity (Table 5).

Discussion

From the beginning of the HIV pandemic, pulmonary complications have been the leading cause of morbidity (5,11). Approximately, 70 % of the affected are suffering from infectious etiologies (6). The epidemiology of infectious diseases varies markedly regarding the prevalent etiology of the region (12). Although with the widespread use of antiretroviral therapies and prophylaxis against opportunistic infections, primary contributors of pulmonary complications are shifting to non-infectious etiologies, respiratory infections remain the leading

Table 5. Comparison among 878 patients concerning cavitary lesion

Parameter	Without cavitary lesion N (%)	With cavitary lesion N (%)	p-value
Age (mean ± SD) (years)	38±10	40±9	0.058
Sex			
Male	656 (89.5%)	142 (97.9%)	0.001*
Female	77 (10.5%)	3 (2.1%)	
HIV status[1]			
New	238 (33.1%)	59 (41.5%)	0.053
Known case	481 (66.9%)	83 (58.5%)	
ART status[2]			
No	507 (72.5%)	107 (78.1%)	0.177
Yes	192 (27.5%)	30 (21.9%)	
History of old TB	197 (26.9%)	47 (32.4%)	0.174
ESR (mean ± SD) (*mm/hr*)	74 ±38	83 ±37	0.014*
$CD4^+$ cell count[3] (mean ± SD) (*cells/mm*^{3})	97±154	118±147	0.150
HIV viral load (mean)	1,045,056	475,955	0.646
Diagnosis accuracy			
Definite	548 (74.8%)	120 (82.8%)	0.001*
Probable	144 (19.6%)	11 (7.6%)	
Unknown	41 (5.6%)	14 (9.7%)	
Mortality	138 (23.2)	27 (24.5)	0.751
Total	733	145	

* Statistically significant difference. 1) Missing data: 18 cases. 2) Missing data: 42 cases. 3) Missing data: 178 cases.
SD: Standard Deviation, HIV: Human Immunodeficiency Virus, ART: Antiretroviral Therapy, TB: Tuberculosis, ESR: Erythrocyte Sedimentation Rate.

etiology of hospital admission in developing countries (5,8,13,14). Various etiologies of infectious diseases are mostly influenced by regional prevalent germs, which in terms would affect the etiology of cavity lesions in the HIV population (12). Furthermore, the efficiency of domestic Health Organizations in early diagnosis and proper antiretroviral coverage of the affected patients plays a key role in the outcome. Examples can be seen in Africa and Eastern Europe with a greater number of TB patients as the prime complication of HIV. Perversely, in Western Europe and North America PJP is the culprit for most HIV complications. Thus, answering the question about the regional epidemiology of HIV complications would facilitate clinicians' treatment struggles (15-17).

In this retrospective study, 844 patients with a median age of 38.7±9.5 years and a total sum of 1000 admissions were enrolled. The foremost important finding of our study is demonstrating TB as the cardinal pulmonary complication of HIV positive patients. For instance, of 145 HIV infected individuals displaying cavity lesions in their plain chest radiography, 105 cases (72.5%) were afflicted with TB. PJP with 7.6% and septic embolism with 5.6% were respectively identified as the second and third most common etiologies. Cavity lesions revealed a significant tendency to involve upper lobes and 57.5% of cases had affected a single lobe. Cavity

lesions were significantly more prevalent among male patients. No significant difference in demographics, HIV and ART status, CD4 positive cell count, viral load, and mortality was evident between the two groups.

Three similar studies had been performed to investigate the complications of HIV. Rodriguez *et al* (18) studied 78 cavitary lesions in 73 HIV positive cases in Spain with a median age of 30 years from 1989 to 1996. Aviram *et al* (19) in the United States investigated 25 HIV patients with cavitary lesions in CT scans, from 1996 to 1998. Lastly, Lin *et al* (20) designed a retrospective survey in Taiwan from 1994 to 2008, describing cavitary lesions in a population of 66 cases aging from 23 to 821 with 73 admission episodes, who were suffering from cavitary lesions as well. Of these patients, 87% were infected by sexual transmission. All mentioned surveys have been performed in considerably past intervals. Given the fact that etiologies of infectious diseases would usually undergo significant variations over time, concerning advances in prevention and treatment schemes, discrepancies in our results are expected. In addition, demographics and patient risk factors play an important role in determining the outcome. For example, in the survey performed in Spain, the majority of patients were intravenous drug abusers, whereas in Taiwan the majority were infected by unprotected sexual contact. IV drug abuse and imprisonment are independent indicators of TB infection. In general, the presenting study investigates a broader group of patients in the current epidemiologic situation in the region. Besides, previous studies were performed during the initial phase of the HIV epidemic and therefore did not consider the role of ART or Co-Trimoxazol prophylaxis as influential variables.

Although cavitary lesions have been seen in PJP, they are not considered to be its prevalent presentation. In our study, of 145 patients with cavity lesions in a plain chest radiograph, 11 were diagnosed with PJP. Perhaps, in the six cases, which were concomitantly infected with PJP and TB, the cavitary lesion could be attributed to the TB component. Yet, in the remaining 5 cases, only for two patients with a definite diagnosis of PJP no other etiology for cavity could be proposed. This implies the fact that although PJP itself is responsible for less than 1.4% of cavity formations, its concurrent incidence with other infections should not be overlooked.

In light of comparison between the two mentioned groups, with and without cavity lesions, it seems lucid that cavitary lesions have a strong correlation with male sex and elevated ESR levels. Perhaps, this could be attributable to the greater prevalence of TB in this population. Moreover, those who had formed cavitary lesions regularly ended up with definitive diagnoses. Similarly, this could be attributable to the frequency of TB diagnosis, regarding the fact that by sputum culture, a definite TB diagnosis is readily available. The presenting study has been performed in a tertiary pulmonary center with complete diagnostic facilities. Therefore, patients were delicately approached until a definitive diagnosis was approved. On the other hand, performing the study in a tertiary center, which is a referral for TB patients, might have interfered with TB estimations. With regard to excessive TB refers to our center the TB prevalence might have been exaggerated. Meanwhile, relatively minor complications, such as CAP might have not been referred to our hospital. As a result, the lower prevalence of CAP in our study could be attributable to its management in some less specific centers.

Conclusion

In conclusion, pulmonary TB has presented to be the cardinal etiology for cavitary lesions in HIV positives, responsible for 72.5% of the lesions. *P. jiroveci* pneumonia, accountable for 7.6% of the cases, and septic emboli affecting 5.6% of the cases were responsible for the second and the third most common complications among HIV affected patients. 58.5% of the cavities had occurred in a single lobe and significantly involved upper zones. Cavitary lesions were considerably more prevalent in the male population.

Sources of support

None.

Conflict of Interest

There is no conflict of interest to declare.

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