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Original Article

AIDS-Related Opportunistic Infections in Hospital Kuala Lumpur

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SUMMARY: We retrospectively reviewed 419 HIV/AIDS patients in Hospital Kuala Lumpur from 1994 to 2001. In the male group, the age range was 20 - 74, with a mean age 37 years, while in the female group it was 17 - 63, with a mean age of 33 years. With regard to age group, it was found that the preponderant age group was 25 - 34 years. The majority of male subjects were Chinese (52.5%), single (56.3%), and unemployed (55.1%), whereas the females were Malay (42.3%), married (79.5%), and non-laborer (64.1%). Also, both groups resided in Kuala Lumpur and had heterosexual contact as the leading cause of HIV transmission. More than half of the patients had CD4 cell counts of <200 cells/cumm. We found that the acquisition of HIV infection via intravenous drug use (IDU) was directly related to the incidence of tuberculosis infection ($P < 0.05$). Further analysis showed HIV-related tuberculosis with IDU was also dependently correlated with occupational status (unemployed) ($P < 0.05$). The four main AIDS-defining diseases include tuberculosis (48%), *Pneumocystis carinii* pneumonia (13%), toxoplasmic encephalitis (11%), and cryptococcal meningitis (7%); in addition, 53% of these patients were found to have CD4 cell counts of less than 200 cells/cumm at the time of diagnosis.

INTRODUCTION

Since the start of the epidemic, issues related to HIV/AIDS have had a high profile in industrialized countries. However, the burden of disease continues to fall most heavily, and often less visibly, in developing countries, particularly in Africa (1). The first case of AIDS in Malaysia was reported in 1986; since then the incidence of HIV/AIDS patients has dramatically increased from 200/2 in 1989, 3,393/105 in 1994, to 5,107/1,168 in 2000. Moreover, the number of AIDS death cases are directly proportional to the overall incidence, with one death in 1989, 80 deaths in 1994, and 882 deaths in 2000 (2). The opportunistic infections, therefore, play as a major role in clinical presentations and remain one of the most frequent causes of death in these patients. The purposes of this study were to determine the frequency and type of major opportunistic infections in AIDS patients, and to determine the association of opportunistic infections with risk factors at the time of diagnosis among these patients in Hospital Kuala Lumpur (HKL) in order to accumulate up-to-date information that will lead to a greater awareness and management of this modern day "plague" and its complications.

MATERIALS AND METHODS

Patients: This retrospective and descriptive study was carried out at the Out-Patient Department for infectious diseases in HKL, which has 2,502 beds and is the largest government tertiary referral hospital, primarily focusing on public services. There are approximately 30 new and 300 follow-up patients with HIV-infection per month coming to this hospital for medical treatment. We were able to review the medical records of 419 out of 1,700 adult HIV-infected patients from January 1994 to April 2001, who came to this hospital because they were screened for HIV infection at private clinics/other hospitals or they developed symptoms presumed to be HIV infection. Their symptoms of HIV disease were examined, and their records were screened for demographic profiles (such as age, sex, race, marital status, occupation, and present address), risk factors for HIV transmission, and clinical and laboratory data.

Patients with CD4 cell counts <200 cells/cumm received trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP), while prophylactic treatments for other opportunistic infections were not given. In Malaysia, zidovudine has been available since 1989, and other antiretroviral drugs including protease inhibitors have been available since 1997. Patients began to be treated with one of the antiretroviral drugs such as zidovudine when they had CD4 cell counts <200 cells/cumm or when they were determined to have symptomatic AIDS-related opportunistic diseases. Of the 419 patients included in this study, 83.5% (350/419) were prescribed antiretroviral drugs, monotherapy, or double or triple-drug therapy (highly active antiretroviral therapy [HAART]); the others may not have met the criteria or have had access to antiretroviral drugs, primarily due to cost.

Diagnoses of opportunistic diseases: Ziehl-Neelsen staining and culture were performed when tuberculosis (TB) was suspected. Cases of TB were classified as definite, probable, or possible: 7% (10/135) were classified as definite cases if the culture for *Mycobacterium tuberculosis* was positive; 30% (40/135) as probable cases if clinical symptoms and signs were present and a stain was positive for acid fast bacilli, or histological findings were consistent with TB; and 56% (75/135) as possible cases if clinical symptoms and signs with X-ray findings were consistent with TB and there was improvement with the standard anti-tubercular therapy. Thirty-six cases of PCP were diagnosed solely by clinical

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symptoms and signs as well as CXR findings after the possibility of other infections was eliminated by instilling anti-PCP therapy. Toxoplasmic encephalitis (TE) was diagnosed in the presence of at least two of the following findings: a history of neurological symptoms; neurological signs at admission, or suggestive computed tomography (CT), all associated with the introduction of anti-TE (fansidar + clindamycin/dapsone) therapy: 69% (22/32) were diagnosed by clinical symptoms and signs, CT scan findings, and a positive test for anti-*Toxoplasma* (IgG) antibodies, which were detected by a serological ELISA commercial kit, while 31% (10/32) were diagnosed only by clinical symptoms and signs and CT scan findings without anti-*Toxoplasma* antibody status. In this hospital, all cases of cryptococcal meningitis were diagnosed based on clinical symptoms and signs as well as the antigen detection test, which employs the ELISA test and uses either serum or cerebrospinal fluid. Twenty-seven cases of pneumonia, including bacteria and *Mycobacterium avium* complex (MAC) infections, were diagnosed on a clinical basis, CXR findings, stain and/or blood culture in order to rule out the underlying cause of the organisms. For the diagnosis in five cases of cytomegalovirus (CMV) retinitis, an opthalmologist examined the patients at regular intervals. In the case of cryptosporidiosis, a diarrheal stool was sent to a special parasitology laboratory, where modified procedures for acid-fast staining of stool concentrates were performed. Histological findings were used to confirm the diagnosis of disseminated endemic fungal infections, which included six cases each of histoplasmosis, penicillosis, and four cases with malignancy. The clinical appearances were the primary basis of diagnoses for all cases of oral candidiasis and oral hairy leukoplakia; in addition, esophagoscopy was used for confirmation in 10 cases of esophageal candidiasis. The other opportunistic diseases, including herpes infections and scabies, were primarily diagnosed on clinical grounds while serological diagnosis was used to detect hepatitis B and C infections. AIDS-defining illnesses were also based on the 1993 Centers for Disease Control and Prevention (3), but the criteria for CD4 cell counts were not used.

Statistical analysis: The data was analyzed by using the statistical software, SPSS version 10 (SPSS Inc, Chicago, Ill., USA). The data with quantitative variables are expressed as median and range, while qualitative variables are expressed as frequency and percentage. Statistical analysis was carried out using either the Chi-square test or Fisher's exact test, as appropriate. A *P*-value of <0.05 was regarded as statistically significant.

RESULTS

Table 1 shows the patient demographic and baseline characteristics at the time of this study. In the male group, the age range was 20 - 74, with a mean age 36.95 years, while in the female group it was 17 - 63, with a mean age of 32.85 years. With regard to age group, it was found that the preponderant age group was 25 to 34 years. The majority of male subjects were Chinese (52.5%), single (56.3%), and unemployed (55.1%), whereas, the females were Malay (42.3%), married (79.5%), and non-laborer (64.1%). Also, both groups resided in Kuala Lumpur and had heterosexual contact as the leading cause of HIV transmission.

We detected that the acquisition of HIV infection via IDU was directly related to the incidence of TB infection ($P < 0.05$), and further analysis showed HIV-related TB with IDU was also dependently correlated with occupational status (unemployed) ($P < 0.05$), as shown in Table 2.

Table 1. Demographic and baseline characteristics of the study subjects

Characteristics		Male (%) *n* = 341	Female (%) *n* = 78
Range of age		20 - 74 y	17 - 63 y
Median		36.95 y	32.85 y
Sex ratio (M:F) = 4.4:1			
Age group	15 - 24 y	12 (3.5)	13 (16.7)
	25 - 34 y	142 (41.6)	40 (51.3)
	35 - 44 y	130 (38.1)	19 (24.4)
	45 - 54 y	40 (11.7)	2 (0.6)
	≥55 y	17 (5.0)	4 (1.2)
Race	Malay	114 (33.4)	33 (42.3)
	Chinese	179 (52.5)	31 (39.7)
	Indian	46 (13.5)	6 (7.7)
	Others[1)]	2 (0.6)	8 (10.3)
Marital status	Single	192 (56.3)	16 (20.5)
	Married	149 (43.7)	62 (79.5)
Address	Kuala Lumpur	196 (57.5)	52 (66.7)
	Outside	145 (42.5)	26 (33.3)
Occupation	Laborer[2)]	84 (24.6)	10 (12.8)
	Non-laborer[3)]	69 (20.2)	50 (64.1)
	Unemployed	188 (55.1)	18 (23.1)
Risk behavior	Heterosexual	256 (75.1)	74 (95.0)
	Intravenous drug use	149 (43.6)	14 (18.0)
	Homosexual	4 (1.2)	–
	Blood transfusion	9 (2.6)	6 (7.7)
CD4 count (cell/cumm)[4)]	<200	180 (52.8)	42 (53.8)
	≥200	155 (45.5)	35 (44.9)
	Unknown	6 (1.4)	1 (0.2)

[1)]: Others: foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.
[2)]: Laborers included farmers and manual laborers.
[3)]: Non-laborers included government employees, private sector employees, merchants, and housewives.
[4)]: Median CD4 cell count = 179 cells/cumm (range = 0 - 1161 cells/cumm); <200 cells/cumm = 222 (53.0%) patients, ≥200 cells/cumm = 190 (45.3%) patients, Unknown = 7 (1.7%) patients.

Table 3 shows that of the 419 HIV/AIDS patients, 282 developed symptoms of AIDS-defining diseases.

Overall, 15 AIDS indicator illnesses were included, and at least one patient was registered for each of the conditions listed. The most commonly reported opportunistic diseases were TB, PCP, TE, cryptococcal meningitis, and bacterial pneumonia, which were described as follows: TB was the most frequent opportunistic infection, developing in 135 patients (48%). The diagnosis of TB was definite for 10, probable for 40, and possible for 75 of these cases. Of these patients, 59.3% had CD4 cell counts of less than 200 cells/cumm at the time of developing TB. In addition, 82% (111/135) had pulmonary TB, as the most common disease location, 14% (19/135) extra-pulmonary TB, and 4% (5/135) mixed types of TB. No evidence of multidrugs resistance *M. tuberculosis* or dead cases was identified in this study. All other patients responded well to the standard anti-tubercular therapy.

PCP developed in 36 patients (13%); the majority of patients, 81% (29/36), had CD4 cell counts of less than 200

Table 2. The frequency of opportunistic diseases in relation to risk factors of HIV transmission in this study

Opportunistic diseases	Risk factors of HIV transmission (%)				Total
	Heterosexual[1)]	Homosexual[2)]	IDU[3)]	BT[4)]	
Related to bacterial infections					
Tuberculosis[5)]					
Pulmonary	79 (67.5)	–	58 (73.4)	3 (60.0)	140
Extra-pulmonary	16 (13.7)	–	10 (12.7)	–	26
Pulmonary and extra-pulmonary	4 (3.4)	–	2 (2.5)	–	6
Pneumonia, bacterial	11 (9.4)	1 (100.0)	9 (11.4)	2 (40.0)	23
Mycobacterium avium complex infection	7 (6.0)	–	–	–	7
Total	117 (100.0)	1 (100.0)	79 (100.0)	5 (100.0)	202
Related to fungal infections					
Candidiasis					
oral	120 (63.8)	1 (100.0)	39 (75.0)	5 (55.6)	165
esophagus	8 (4.3)	–	4 (7.7)	–	12
Cryptococcal meningitis	19 (10.1)	–	1 (2.1)	–	20
Pneumocystis carinii pneumonia	32 (17.0)	–	6 (11.5)	2 (22.2)	40
Histoplasmosis	4 (2.1)	–	1 (1.9)	1 (11.1)	6
Penicillosis	5 (2.7)	–	1 (1.9)	1 (11.1)	7
Total	188 (100.0)	1 (100.0)	52 (100.0)	9 (100.0)	250
Related to viral infections					
Herpes infection (HS and HZ)[6)]	81 (57.5)	1 (50.0)	20 (26.7)	1 (25.0)	103
Hepatitis C virus infection	30 (21.3)	1 (50.0)	39 (52.0)	2 (50.0)	72
Hepatitis B virus infection	21 (15.0)	–	13 (17.3)	–	34
Oral hairly leukoplakia	5 (3.6)	–	2 (2.7)	1 (25.0)	8
Cytomegalovirus infection	4 (2.8)	–	1 (1.3)	–	5
Total	141 (100.0)	2 (100.0)	75 (100.0)	4 (100.0)	222
Related to parasitic infections					
Cryptosporidiosis	–	–	1 (14.3)	–	1
Ectoparasite: Scabies	6 (17.1)	–	3 (42.9)	–	9
Toxoplasmic encephalitis	29 (82.8)	–	3 (42.9)	–	32
Total	35 (100.0)	0	7 (100.0)	0	42
Related to malignancy					
Kaposi's sarcoma	–	1 (100.0)	–	–	1
Non Hodgkin's lymphoma	2 (66.6)	–	–	–	2
Invasive carcinoma, cervix	1 (33.3)	–	–	–	1
Total	3 (100.0)	1 (100.0)	0	0	4
Others					
Wasting syndrome	1 (50.0)	–	–	–	1
AIDS-dementia	1 (50.0)	–	–	–	1
Total	2 (100.0)	0	0	0	2

[1)]: Heterosexual was presumed if the patient's sex partner was known to have HIV infection or the patient had multiple sexual contacts with prostitutes.
[2)]: Homosexual or MSM was presumed if the patient accepted having sex with men.
[3)]: IDU: intravenous drug use.
[4)]: BT: blood transfusion.
[5)]: Tuberculosis infection was strongly associated with persons who acquired HIV infection via IDU ($P = 0.0001$). Further analysis showed HIV-related tuberculosis with IDU was dependently correlated with occupational status (unemployed) ($P = 0.002$).
[6)]: HS: herpes simplex, HZ: herpes zoster.

cells/cumm. The outcomes of these patients were as follows: 92% (33/36) responded well to the anti-PCP therapy, and 8% (8/36) still required ongoing therapy at the time of this report.

TE developed in 32 patients (11%); more than half of these patients received cotrimoxazole as a primary chemoprophylaxis for PCP. At the time of diagnosis, 69% (22/32) and 28% (9/32) of patients had CD4 cell counts <200 and ≥200 cells/cumm, respectively. The outcome of these patients with 6 weeks anti-TE therapy were 81% (26/32) successfully treated with undergo lifelong anti-TE maintainance, 16% (5/32) treatment continued and 3% (1/32) transferred to other hospitals.

Meningitis was the most common form of disseminated cryptococcosis which developed in 20 patients (7%). All cases were diagnosed by clinical and neurological symptoms and signs with the confirmations of laboratory investigations. The outcome of patients were 90% (18/20) success with the antifungal therapy, 5% (1/20) treatment continued and 5% (1/20) transferred to other hospital.

Others were bacterial pneumonia including MAC infec-

Table 3. The finding of AIDS-related opportunistic infections in relation to CD4 cell count in this study

Opportunistic infections	CD4 cell count (%)			Total
	<200	≥200	Not recorded	*n* = 282
Related to bacterial infections				
Tuberculosis (all types)	80 (59.3)	51 (37.8)	4 (3.0)	135
Pulmonary	66 (60.0)	43 (38.7)	2 (1.8)	111
Extra-pulmonary	11 (58.0)	6 (31.6)	2 (10.5)	19
Pulmonary and extra-pulmonary	3 (60.0)	2 (40.0)	–	5
Pneumonia, bacterial	12 (60.0)	8 (40.0)	–	20
Mycobacterium avium complex infection	6 (85.7)	1 (14.3)	–	7
Related to fungal infections				
Esophageal candidiasis	9 (90.0)	–	1 (10.0)	10
Cryptococcal meningitis	16 (80.0)	2 (10.0)	2 (10.0)	20
Pneumocystis carinii pneumonia	29 (80.6)	7 (19.4)	–	36
Histoplasmosis	5 (83.3)	1 (16.7)	–	6
Penicillosis	6 (100.0)	–	–	6
Related to viral infections				
Cytomegalovirus infection	4 (80.0)	1 (20.0)	–	5
Related to parasitic infections				
Cryptosporidiosis	1 (100.0)	–	–	1
Toxoplasmic encephalitis	22 (69.0)	9 (28.1)	1 (3.1)	32
Related to malignancy				
Kaposi's sarcoma	–	1 (100.0)	–	1
Burkitt's lymphoma	2 (100.0)	–	–	2
Invasive carcinoma, cervix	1 (100.0)	–	–	1
Others				
Wasting syndrome	1 (100.0)	–	–	1

tion in 27 (10%), cryptococcal meningitis in 20 (7%), esophageal candidiasis in 10 (4%), histoplasmosis in 6 (2%), penicillosis in 6 (2%), CMV infection in 5 (2%), malignancy in 4 (1%), cryptosporidiosis in 1 (0.4%), and wasting syndrome in 1 (0.4%). In addition, more than half of these patients had CD4 cell counts less than 200 cells/cumm at the time of diagnosis in this report.

DISCUSSION

In this study, TB was the most common among AIDS-related opportunistic pulmonary diseases. This result is lower than one previous study which showed 56% in the prevalence of TB (4). TB is the leading cause of death in HIV-infected persons globally and accounts for an estimated 44% of all AIDS-related deaths annually (5). TB stands out as the most important causes of the morbidity and mortality in most developing countries (1), but the relative prevalence of the disease shows considerable regional variation i.e., 32% in Brazil (6), 28% in Côte d'lvoire (1), 76% in India (7), 18% in Kenya (8-10), and 28.9% in Thailand (11). It is striking that in almost every study from developing regions, TB is the most frequently identified opportunistic disease (1). Further studies are required to discover new rapid diagnostic methods or effective drugs that can lead to a decline in the incidence of TB and prolong life expectancy in the near future. From the present study, TB infection among persons who have acquired HIV infection via IDU was found to be strongly associated with occupational status (unemployed) ($P < 0.05$) and with CD4 cell counts of less than 200 cells/cumm ($P < 0.05$). The significant impact of TB in HIV infection via IDU has been similarly shown by previous studies (12,13), in which control measures for TB such as anti-tubercular prophylaxis have been effectively implemented among these high-risk patients. In addition, this finding prompts us to realize that even though unemployed individuals are the major group of this population, maintaining a marginal or poor standard of living can lead to unfavorable circumstances increasing the chance of exposure to this contagious disease. It would be interesting to investigate the socioeconomic risk factors associated with TB, after adjusting for HIV, in different settings. The role of management in terms of early diagnosis and proper treatment, including anti-tubercular drugs along with HAART, should be emphasized in order to improve the immunosuppressive status where CD4 cell counts play a crucial role in complicating the advent of AIDS.

Our data show that PCP was the second most common opportunistic disease among AIDS patients; moreover, the majority of the patients in this study, 80.6% (29/36), still had CD4 cell counts of less than 200 cells/cumm. Interestingly, the frequency of PCP has decreased remarkably, as studies have shown in both developed and developing countries. This decrease may generally be due to a combination of chemoprophylaxis with anti-retroviral therapy, and most diagnoses being made on clinical ground alone; therefore, the figures may not accurately reflect the true incidence of PCP infection, and the early AIDS-related mortality due to other causes may reduce the rates of this disease (11). Meanwhile the 80.0% (16/20) of patients with cryptococcal meningitis had CD4 cell counts of less than 200 cells/cumm in this study. The decline in the prevalence of cryptococcal infection may be due to the impact of antifungal agents either as treatment or prophylaxis to other common opportunistic fungal infections such as oral candidiasis. Moreover, the CD4 cell counts still

increase the risk of infection, as has been supported by other studies (14,15). We found only 10 cases of esophageal candidiasis that were regarded to be the most common disseminated form of candidiasis found in AIDS-defining illness (16). Nevertheless, in patients with AIDS, the identification of opportunistic esophageal disease portends a poor prognosis (17), as well as the possible emergence of strains resistant to antifungal drugs and high therapy costs. We therefore suggest that the prophylactic maintenance therapy should be administered to AIDS patients with frequent symptomatic relapses of esophageal candidiasis (18).

Interestingly, we observed that TE was the third most common opportunistic disease in these patients. In general, *Toxoplasma gondii* is a ubiquitous, intracellular protozoan parasite that exists in and infects as a latent stage approximately half of the world population. TE is due to recrudescence of a chronic or latent *Toxoplasma* infection as a result of the progressive loss of cellular immune surveillance (19). TE is the most common clinical disease entity due to toxoplasmosis (20), and the most frequent cause of focal intracerebral lesions in AIDS patients (21). The incidence of TE is therefore directly proportional to the prevalence of antibodies to *Toxoplasma* in any given population (20). In the present study, most patients, 68.8% (22/32), had CD4 cell counts of less than 200 cells/cumm at the time they developed TE, furthermore, we verified that in those patients with CD4 cell counts that fell below 100 cells/cumm, 53.1% (17/32) also had TE. This finding is in agreement with previous reports (22-26), we therefore suggest that there be routine screening for *Toxoplasma* serology and primary anti-TE prophylaxis for all HIV-positive patients so as to reduce the incidence of TE, which is likely to occur in these patients.

In conclusion, the distribution of AIDS-related opportunistic infections in Malaysia indicates the beneficial clinical significance of efforts to prevent or treat the more common local or systemic opportunistic infections. In addition, public health efforts to prevent HIV infection should be highlighted, as the importance of preventing and treating AIDS-related opportunistic infections in Malaysia is likely to increase.

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