SPECTRUM OF OPPORTUNISTIC INFECTIONS AMONG HIV-INFECTED PATIENTS IN MALAYSIA

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Abstract. We retrospectively reviewed 205 HIV-infected patients, who came at first entry from January 2001 to December 2002 to the Hospital Kuala Lumpur, Kuala Lumpur, Malaysia. The aged range was 21-69 years [mean 37.25 years (±SD) 8.1]. Subjects were mainly in the age group 35-44 years. The majority of patients were male (82%), Chinese (55.1%), single (55.6%), resided in Kuala Lumpur (55.1%), and were unemployed (57.1%). The most frequent routes of transmission were sexual contact (78.5%), followed by IDUs (30%), blood transfusion (5%), and unknown (0.5%). Oral candidiasis was the most common muco-cutaneous disease and significant co-existence was found with the main opportunistic systemic diseases, such as TB, PCP, toxoplasmic encephalitis, penicillosis, and CMV retinitis ($p<0.05$). In this study, the range of CD4 counts was 0-910, with a median of 35 cells/mm^3. Significant associations between a CD4 level less than 100 cells/mm^3 at the time of diagnosis, and the occurrence of major opportunistic diseases, such as candidiasis, TB, PCP, TE, herpes simplex infection, CMV retinitis, penicillosis, and histoplasmosis were found ($p<0.05$) in this study.

INTRODUCTION

The HIV/AIDS pandemic is still a major health problem particularly challenging developing countries. In Malaysia, the number of HIV/AIDS patients has increased from 200/1 cases in the years 1990 to 4,198/233 cases in the year 1995, and 5,107/1,168 cases by the year 2000, while the number of deaths has also markedly increased in the same period, from 1 case in 1990 to 165 cases in 1995, and 882 in 2000 (Ministry of Health, Malaysia, 2000). The relative frequencies of specific opportunistic diseases may vary in different countries, since the prevalence of microorganisms in a given environment determines the patterns of invading pathogens and latent infections (Oh *et al*, 1999). The aims of this study were to determine the incidence of opportunistic diseases among HIV-infected patients, to determine the significant co-existence between oral candidiasis and opportunistic systemic diseases, and to determine the association between the presence of opportunistic diseases and the levels of CD4 counts of less than 100 cells/mm^3 to justify the pattern of opportunistic disease among HIV-infected patients in this hospital.

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MATERIALS AND METHODS

Patients

This retrospective and descriptive study was carried out at the Out-Patient Department (OPD) for infectious diseases in the 2,502 bed Hospital Kuala Lumpur (HKL), the largest government tertiary referral hospital in Malaysia mainly focusing on public services. About 30 new and 300 follow-up patients with HIV infection per month come for medical treatment in this hospital. A total of 559 HIV-infected patients, who came at first entry from January 2001 to December 2002, were consecutively reviewed. Only 205 patients were classified as symptomatic HIV or full-blown AIDS patients at the time of diagnosis. They came to this hospital because they were screened for HIV infection at private clinics/other hospitals, or developed symptoms presumed to be HIV infection. They were examined for symptoms of HIV disease, and their records were screened for demographic profile (such as age, sex, race, marital status, occupation and present address), risk factors for HIV transmission, and clinical and laboratory data.

In Malaysia, zidovudine has been available since 1989, and other antiretroviral drugs, including protease inhibitors, since 1997. Patients were treated first with one of the antiretroviral drugs, such as zidovudine, when they had CD4 cell counts < 200 cells/mm^3 or when they had symptomatic AIDS-related opportunistic diseases. Of the 205 patients included in this study, 86% (177/205) were prescribed antiretroviral drugs: 7% (15/205) monotherapy, 2% (4/

205) double, 44% (91/205) triple-drug (HAART) therapy, whereas others did not meet the criteria or could access antiretroviral drug therapy due mainly to its cost. Patients with CD4 cell counts < 200 cells/mm^3 received trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP), while prophylactic treatments for other opportunistic infections were not given.

Diagnoses of opportunistic diseases

Tuberculosis was defined as a patient in whom tuberculosis had been bacteriologically confirmed, or had been diagnosed by a clinician. The definitions of pulmonary and extrapulmonary tuberculosis were those used by the World Health Organization (2002a). 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 therapy (fansidar+clindamycin/dapsone). Using the same form, we analyzed files from AIDS patients with other CNS infections, such as cryptococcosis, primary CNS lymphoma and tuberculosis, for correction of finally undefined bias. A good therapeutic response was defined as improvement of clinical condition, regression of neurological signs and symptoms, or improvement of CT scan. The other opportunistic diseases, including PCP, were diagnosed according to criteria suggested by the Centers for Disease Control and Prevention; AIDS defining illnesses were also based on the 1993 CDC, but the criteria for CD4 cell counts were not used.

Statistical analysis

The data were analyzed by the statistical software, SPSS version 10 (SPSS Inc, Chicago, USA). Data with quantitative variables were expressed as mean (±SD) and range, while qualitative variables were expressed as frequency and percentage. Statistical analysis was performed using either chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was regarded as statistically significant.

RESULTS

Patient characteristics

The age range was 21-69 years, with a mean of 37.25 ± 8.1. Subjects were mainly in the age group 35-44 years. The sex ratio was (M:F) 4.5:1. The majority of patients was male (82%), Chinese (55.1%), single (55.6%), resident in Kuala Lumpur (55.1%), and unemployed (57.1%). The most frequent routes of transmission were sexual contact (78.5%), followed by IDUs (30%), blood transfusion (5%), and unknown (0.5%), as shown in Table 1.

Opportunistic infections

The frequency distribution of opportunistic infections in 205 HIV-infected patients is shown in Table 2. Candidiasis was the most common initial

Table 1
Demographic and baseline characteristics of 205 HIV-infected patients.

Characteristics	Total no. of patients (%)
Range of age = 21-69 years	
Mean ± SD = 37.25 ± 8.1 years	
Sex ratio (M:F) = 4.5:1	
Age group	
15-24	5 (2.4)
25-34	78 (38)
35-44	83 (40.5)
≥ 45	39 (19)
Sex	
Male	168 (82)
Female	37 (18)
Race	
Malay	70 (34.2)
Chinese	113 (55.1)
Indian	15 (7.3)
Others[a]	7 (3.4)
Marital status	
Single	114 (55.6)
Married	91 (44.4)
Address	
Kuala Lumpur	113 (55.1)
Outsider	92 (44.9)
Occupation	
Laborer[b]	39 (19)
Non-laborer[c]	49 (24)
Unemployed	117 (57.1)
Risk behavior	
Heterosexual	154 (75.1)
Homosexual	7 (3.4)
Intravenous drug use	61 (30)
Blood transfusion	10 (5)
Unknown	1 (0.5)

[a] Others: foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.
[b] Laborer included farmer and manual laborer.
[c] Non-laborer included government employee, private sector, merchant and housewife.

Table 2
Incidence of opportunistic infections in 205 HIV-infected patients attending Hospital Kuala Lumpur, January 2001 - December 2002.

Clinical conditions	No. (%) of patients	
	Initial presentation	Overall
Bacteria		
Tuberculosis[a]	83 (40.5)	93 (45.4)
Pulmonary and disseminated tuberculosis	53 (26)	58 (28.3)
Extrapulmonary tuberculosis and disseminated	30 (14.6)	35 (17.1)
Bacterial pneumonia	2 (1)	2 (1)
Splenic abscess	1 (0.5)	1 (0.5)
Norcardiasis	1 (0.5)	1 (0.5)
Septicemia (*Staphylococcus aureus, Salmonella* spp)	4 (2)	4 (2)
Bronchopneumonia	1 (0.5)	1 (0.5)
Lung abscess	1 (0.5)	1 (0.5)
Fungal		
Candidiasis	98 (47.8)	99 (48.3)
Oral[a,b]	88 (43)	89 (43.4)
Esophageal	10 (5)	10 (5)
Pneumocystis carinii pneumonia[a]	25 (12.2)	25 (12.2)
Cryptococcal meningitis	6 (3)	6 (3)
Penicillosis[b]	5 (2.5)	5 (2.5)
Histoplasmosis	3 (1.5)	3 (1.5)
Others	2 (1)	2 (1)
Parasitic		
Toxoplasmic encephalitis[a]	18 (8.8)	18 (8.8)
Scabies	2 (1)	2 (1)
Viral		
Hepatitis C virus (serodiagnosis)	59 (28.8)	59 (28.8)
Hepatitis B virus (serodiagnosis)	17 (8.3)	17 (8.3)
Herpes zoster	10 (5)	10 (5)
Herpes simplex	7 (3.5)	7 (3.5)
Cytomegalovirus disease[b]	6 (3)	6 (3)
Human papilloma virus	5 (2.5)	5 (2.5)
Others		
Syphilis (serodiagnosis)	9 (4.4)	9 (4.4)
Papulopruritic eruption	3 (1.5)	3 (1.5)
Seborrheic dermatitis	3 (1.5)	3 (1.5)
Psoriasis	2 (1)	2 (1)
Ichthyosis	1 (0.5)	1 (0.5)
Wasting syndrome	1 (0.5)	1 (0.5)

[a] $p<0.001$; [b] $p<0.05$

(98; 47.8%) and overall (99; 48.3%) opportunistic infection; 43.4% (89/205) of patients had oral candidiasis (88 cases for initial, and 1 case for later presentation), whilst 5% (10/205) of them had esophageal candidiasis. The study revealed a strong co-existence between oral candidiasis and opportunistic systemic diseases such as TB, toxoplasmic encephalitis, PCP, penicillosis, and CMV retinitis ($p<0.05$).

Tuberculosis was the second most frequent opportunistic infection, with 93 (45.4%) patients. 28.3% (58; 53 for initial and 5 for later presentation) of patients had pulmonary tuberculosis (PTB), of

whom 49 had TB-lung and 9 had TB-lung with disseminated form. 17.1% (35; 30 cases for initial and 5 cases for later presentation) patients had extra-pulmonary tuberculosis (EPT). The most common organ involvements were lymph node (20), followed by miliary/disseminated (8), brain (2), skin (2), spine (2), and abdomen (1). Of the 93 TB patients, 21 (23%) were confirmed by tissue biopsy, 14 (15%) by smear positive for acid-fast bacilli (AFB) and/or culture positive for *M. tuberculosis*, and 60 (65%) of them whom 23 cases were diagnosed clinically, while 37 cases were diagnosed by clinical presentation and CXR findings consistent with active tuberculosis. Fifty-four patients had the CD4 cell counts < 100 cells/mm^3. No relapse case was notified, however, MDR-TB was isolated from 1 patient. Five patients were lost to follow-up, and 1 patient died due to advanced tuberculosis. All other patients responded well to standard anti-tubercular therapy.

Pneumocystis carinii pneumonia (PCP) developed in 25 patients (12.2%); 10 cases were diagnosed by clinical presentation and CXR finding, while 15 cases were based on clinical grounds only. In medical practice, trimethoprim-sulfamethoxazole is given to all HIV-infected patients with CD4 counts < 200 cells/mm^3 as primary chemoprophylaxis. Twenty patients had CD4 cell counts of < 100 cells/mm^3 at diagnosis. Most of them were in the advanced stages of AIDS (median CD4 count, 16.5 cells/mm^3).

Toxoplasmic encephalitis (TE) developed in 18 patients (8.8%); more than half of these received cotrimoxazole as primary chemoprophylaxis for *P. carinii* pneumonia. Anti-*Toxoplasma* (IgG) antibodies were found positive in 9 patients, negative in 3 patients, and not known in 6 patients. Fourteen patients had CD4 cell counts < 100 cells/mm^3 at diagnosis. Recurrent TE was identified only in 1 patient, otherwise, all other patients were successfully treated with the standard 6-week anti-TE therapy and lifelong anti-TE maintenance.

Herpes infections developed in 17 (8.5%) patients; 10 (5%) and 7 (3.5%) of the patients had herpes zoster and simplex, respectively. Twelve (6%) patients had either cryptococcal meningitis (6; 3%) or cytomegalovirus infection with commonly involved retina (6; 3%). Penicillosis was recorded in 5 (2.5%) cases, while 3 (1.5%) patients were confirmed with histoplasmosis. Other opportunistic diseases were also identified in this study.

Routine serodiagnostic screenings were performed and noted in patients' medical records in this hospital; the majority of patients (78; 38%) were positive for anti-*Toxoplasma* antibody, followed by 59 (28.8%) for hepatitis C virus infection, among whom more than half coincided with intravenous drug use, 17 (8.3%) for hepatitis B virus infection, and 9 (4.4%) for syphilis by RPR.

First AIDS-defining diseases

Of the 205 patients, tuberculosis was found in 93 (45.4%) cases, *Pneumocystis carinii* pneumonia in 25 (12.2%), toxoplasmic encephalitis in 18 (8.8%), esophageal candidiasis in 10 (5%), herpes simplex in 7 (3.5%), cryptococcal meningitis in 6 (3%) cytomegalovirus in 6 (3%), penicillosis in 5 (2.5%), histoplasmosis in 3 (1.5%) patients, and wasting syndrome in 1 (0.5%) patient. In this study, the range of CD4 counts was 0-910 with a median of 35 cells/mm^3. An association was found between a CD4 level <100 cells/mm^3 and the occurrence of major opportunistic diseases, such as candidiasis, TB, PCP, TE, herpes simplex infection, CMV retinitis, penicillosis, and histoplasmosis ($p<0.05$), as shown in Table 3.

DISCUSSION

Attention is drawn to oral candidiasis as the most common muco-cutaneous disease (43.4%) in this study. This observation is supported by previous studies (Lim *et al*, 2001; Anteyi *et al*, 2003; Reichart *et al*, 2003). This suggests the existence of the disease in every part of the world, even though it may vary in geographical distribution. The study revealed a strong co-existence between oral candidiasis and opportunistic systemic diseases, such as TB, toxoplasmic encephalitis, PCP, penicillosis, and CMV retinitis ($p<0.05$). This suggests that oral candidiasis may be used as a clinical marker or the need for more intensive clinical and laboratory monitoring and possibly initiation of prophylaxis against these opportunistic diseases (Nittayananta *et al*, 2002). However, drug resistance should be seriously considered, particularly in tuberculosis, before use. The majority of patients who developed oral candidiasis had significantly low level CD4 cell counts (<100 cells/mm^3), and had acquired immunodeficiency syndrome (AIDS) defining illness. Therefore, we concluded that muco-cutaneous finding might be a useful clinical indicator or screening tool in the progression of HIV infection with severe immunosuppression (Jing and Ismail, 1999; Ranganathan *et al*, 2000) or signs of the presence of an AIDS defining condition.

Our study showed that tuberculosis was the most frequent opportunistic systemic disease among HIV-infected patients. Tuberculosis is still the main

Table 3
Relationship between 205 HIV-related opportunistic diseases and CD4 cell count at the time of diagnosis.

Opportunistic diseases	No. of patients (%)		
	CD4 <100	CD4 ≥100	Not recorded
Related to bacterial infections			
Tuberculosis[a] (93)	54 (26.3)	35 (17.1)	4 (2)
Pulmonary and disseminated tuberculosis	35 (17.1)	19 (9.3)	4 (2)
Extrapulmonary tuberculosis and disseminated	19 (9.3)	16 (7.8)	-
Bacterial pneumonia	1 (0.5)	1 (0.5)	-
Splenic abscess	1 (0.5)	-	-
Norcardiasis	1 (0.5)	-	-
Septicemia (*Staphylococcus aureus, Salmonella* spp)	2 (1)	2 (1)	-
Bronchopneumonia	-	-	2 (1)
Lung abscess	1 (0.5)	-	-
Related to fungal infections			
Candidiasis [a] (99)	74 (36.1)	20 (10)	5 (2.4)
Oral	65 (31.7)	19 (9.3)	5 (2.4)
Esophageal	9 (4.4)	1 (0.5)	-
Pneumocystis carinii pneumonia [a]	20 (10)	4 (2)	1 (0.5)
Cryptococcal meningitis	4 (2)	2 (1)	-
Penicillosis [b]	4 (2)	1 (0.5)	-
Histoplasmosis [b]	3 (1.5)	-	-
Other fungal infections	-	-	2 (1)
Related to parasitic infections			
Toxoplasmic encephalitis [a]	14 (6.8)	3 (1.5)	1 (0.5)
Scabies	2 (1)	-	-
Related to viral infections			
Herpes zoster	3 (1.5)	6 (3)	1 (0.5)
Herpes simplex [b]	5 (2.5)	2 (1)	-
Cytomegalovirus disease [b]	5 (2.5)	1 (0.5)	-
Human papilloma virus	4 (2)	1 (0.5)	-
Others			
Papulopruritic eruption	2 (1)	-	-
Seborrheic dermatitis	2 (1)	1 (0.5)	-
Psoriasis	1 (0.5)	-	1 (0.5)
Ichthyosis	1 (0.5)	-	-
Wasting syndrome	1 (0.5)	-	-

[a] $p < 0.001$; [b] $p < 0.05$

resurgent co-infection with HIV in Malaysia; moreover, TB/HIV is considered one of the top five communicable diseases in terms of incidence rate in this country being only 6 reported cases in 1990, to 933 cases or 6.5% of the total number of reported cases in 2002 (Ministry of Health, Malaysia, 2002). This figure indicates the direct numerical proportion in number of this dual infection, which may particularly be seen in most developing countries (Glynn, 1998; Murray *et al*, 1999; Siriarayapon *et al*, 2002). Interestingly, the presentation of tuberculosis in these patients varied according to CD4 cell count; nonetheless, more than half of those developed tuberculosis when they had very low CD4 counts. Therefore, early antiretroviral therapy in combination should be recommended in HIV-infected patients to ensure optimal immune system function that limits mortality and morbidity (Mayor *et al*, 2001). Overall, the role of treatment for tuberculosis is quite promising when compared with similar studies, and only 1 case

of MDR-TB was recorded in this study. A recent regional survey showed that the incidence of MDR-TB: resistance to isoniazid and rifampicin, among newly diagnosed tuberculosis cases, was 0.1% among Malaysian patients in 1999 (WHO, 2002b). In fact, Malaysia is at an intermediate level of tuberculosis prevalence, and has adequate health care infrastructure, laboratory services, and regular supplies of anti-tubercular drugs.

We observed that the number of patients with PCP was much lower than tuberculosis in our study, and none was receiving primary prophylactic treatment for PCP. This may be due to their unknown HIV serostatus, or their being lost to follow-up. However, other systemic fungal diseases, such as cryptococcal meningitis, penicillosis, or histoplasmosis also showed the same trend in our patients but still commonly seen in previous studies (Sirisanthana, 1997; Chariyalertsak *et al*, 2001; French *et al*, 2002; Ranjana *et al*, 2002). The possible explanations in the reduction of all AIDS-defining illnesses could be routine primary chemoprophylaxis for PCP and/or the combination of antiretroviral therapy that includes protease inhibitors, as reported in earlier studies (Palella *et al*, 1998; Gatanaga, 2002; Lubis *et al*, 2003).

The study showed that toxoplasmic encephalitis was one of the most common first AIDS-defining disease and occurred particularly when there was a very low CD4 count. These findings are consistent with those of other investigators (Mariuz *et al*, 1997; Skiest, 2002). The prevalence of *Toxoplasma gondii* antibodies among our patients was 38%. Malaysians do own pets, particularly the Malays, who have a habit of very close contact with cats, which is most likely the cause of *Toxoplasma* transmission (Nissapatorn *et al*, 2003). Nevertheless, primary chemoprophylaxis and standard anti-*Toxoplasma* therapy play an important role in controlling this disease, but recurrence of TE can still be seen in our, and other studies. Life-long anti-*Toxoplasma* maintenance is a matter of choice, however, up to 40% of patients discontinued because of adverse reactions (Leport *et al*, 1988). Atovaquone seems to be a promising drug to combat or eradicate the organism; however, one study showed failure in treating TE (Durand *et al*, 1995). At the present time, it is, therefore, a good opportunity for us to move toward the development of newer anti-*Toxoplasma* agents.

In conclusion, our study is limited by the small number patients (205). However, a much larger scale similar study should be conducted, for a better understanding of the management and control of these opportunistic diseases among HIV/AIDS patients. Nevertheless, the effectiveness of HAART therapy currently seems to be promising for lowering the incidence of opportunistic diseases.

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