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Clinical presentations and virologic characteristics of primary human immunodeficiency virus type-1 infection in a university hospital in Taiwan

Hsin-Yun Sun[1], Mei-Jyh Chen[1], Chien-Ching Hung[1,2], Mao-Yuan Chen[1], Szu-Min Hsieh[1], Wang-Huei Sheng[1], Chi-Tay Fang[1], Sui-Yuan Chang[3], Shan-Chwen Chang[1]

[1]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei; and Departments of [2]Parasitology and [3]Medical Technology, National Taiwan University College of Medicine, Taipei, Taiwan, ROC

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Clinical manifestations of primary human immunodeficiency virus (HIV) infection (acute retroviral syndrome) and virologic characteristics of HIV-1 have rarely been described in Taiwan. Medical records of patients followed at the National Taiwan University Hospital between June 1994 and September 2003 were retrospectively reviewed to identify HIV-infected patients who were diagnosed with primary HIV infection. Blood specimens obtained at the diagnosis of primary HIV infection were submitted for viral subtyping and genotypic resistance assay. Twenty out of 940 patients were diagnosed with acute retroviral syndrome during the study period. All of the patients were males, with a median age of 31 years (range, 23 to 42 years); all were men who had sex with men. The most common clinical manifestations were fever (95%), generalized lymphadenopathy (75%), pharyngitis (70%), skin rashes (70%), and gastrointestinal symptoms (60%) including nausea, vomiting, and diarrhea. Thrombocytopenia (35%), leukopenia (35%), and elevated liver function test (50%) were seen in the laboratory tests. The median CD4 lymphocyte count was 312 cells/μL (range, 112-520 cells/μL), and the plasma HIV RNA load by reverse transcriptase-polymerase chain reaction was 230,500 copies/mL (range, 602->750,000 copies/mL). No major resistance mutations on protease or reverse transcriptase were identified in the 11 available viral isolates. We conclude that primary HIV infection was rarely diagnosed in the designated hospital for HIV care in Taiwan. More education of health care providers and counseling of persons at risk to increase awareness of HIV infection are urgently needed in Taiwan in order to facilitate earlier diagnosis of primary HIV infection and prevent further transmission.

Key words: CD4 lymphocyte count, diagnosis, HIV-1, risk factors, viral load

After the initial recognition of the acquired immunodeficiency syndrome (AIDS) in United States in 1981, HIV (human immunodeficiency virus) infection was introduced into Asia in the mid-1980's, with the case number increasing over the following years. According to the report of the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), there were 4.6 to 8.2 million people living with HIV/AIDS at the end of 2003 in south and southeast Asia; 610,000 to 1.1 million cases were newly diagnosed with HIV infection and 330,000 to 590,000 patients died from HIV/AIDS during 2003 [1]. The region was second only to sub-Saharan Africa in terms of incidence, and the case number is still growing in most of the Asian countries.

Corresponding author: Dr. Sui-Yuan Chang, Department of Medical Technology, National Taiwan University College of Medicine, Taipei, Taiwan, ROC.
E-mail: sychang@ha.mc.ntu.edu.tw

In Taiwan, the number of patients with HIV infection is still increasing at a rate of 15 to 20% yearly according to the estimate of Center for Disease Control, Department of Health, Taiwan [2]. The increase might have been related to delayed diagnosis of HIV infection and to further transmission of HIV without appropriate and timely counseling. Symptoms of primary HIV infection are nonspecific and difficult to diagnose [3], and the infection often goes undetected.

Primary HIV infection may play an important role in HIV transmission due to high titers of circulating viruses [4] and patients' unawareness of being infected while maintaining high-risk behaviors. Therefore, it is crucial for health care providers to become aware of the symptoms suggestive of primary HIV infection in order to make the correct diagnosis and interrupt HIV transmission. In this study, we aimed to review the clinical presentations and virological characteristics of

primary HIV infection in patients diagnosed at a referral hospital for HIV care.

Methods

Study population

National Taiwan University Hospital (NTUH) has been the largest referral medical center for the management of HIV-associated complications in Taiwan. Over the past 9 years, there were more than 940 HIV-infected patients seeking medical attention at this hospital, and most were referred at late stage of HIV infection [5]. A retrospective review of medical records of the patients followed at the NTUH was initiated using a standardized case record form to collect demographics; sexual preference; clinical presentations; HIV-related complications; results of laboratory tests, including plasma HIV RNA load and CD4+ and CD8+ lymphocyte count; and date and type of antiretroviral therapy initiated between June 1994 and September 2003.

Definitions

Primary HIV infection was defined as patients with simultaneously positive plasma HIV RNA and negative HIV antibody; probable case as patients with positive HIV antibody presenting symptoms consistent with primary HIV infection [3], and exclusion of other possible etiologies, for example, Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

Virologic investigations

Quantification of PVL was conducted using reverse transcriptase-polymerase chain reaction (RT-PCR) [Roche Amplicor, Version 1.5, Branchburg, NJ, USA] with a lower detection limit of 400 copies/mL. Viral subtyping and genotypic resistance testing were performed for 11 blood specimens obtained at the time when primary HIV infection was diagnosed. Briefly, viral RNA from plasma of HIV-infected patients was extracted using QIAamp viral RNA mini kit (Qiagen, GmbH, Germany). A 1.2-kb DNA fragment corresponding to part of the *pol* gene was amplified by RT-PCR and its nucleotide sequence was determined by ABI 377 autosequencer. For subtype analysis, the sequences were subjected to the phylogenetic tree analysis by the neighbor-joining method and the Kimura 2-parameter distance matrix in the MEGA analytical software [6]. For drug resistance genotypic analysis, the derived amino acid sequence was classified as mutant or non-mutant relative to the consensus for HIV-1 subtype B and sequence analysis from previous reports [7-9]. Strains with mixtures of wild-type and mutant sequences at the indicated amino acid sites that code for drug resistance were considered as drug-resistant.

Results

Between June 1994 and September 2003, 20 patients diagnosed with primary HIV infection were enrolled in this study. All the patients were men who had sex with men, with a median age of 31 years (range, 23 to 42 years); 18 of 20 patients (90%) were homosexuals, and 2 (10%) bisexuals. Most of the cases (17, 85%) were diagnosed after 2000, and only 3 (15%) were diagnosed before 2000 (Table 1).

Table 1. Clinical characteristics of 20 patients with primary HIV infection

Characteristic	Value
Age (years) [median (range)]	31 (23-42)
Male	20
Route of transmission (%)	
Homosexual	90
Heterosexual	0
Bisexual	10
Duration of symptom (days) [median (range)]	19 (5-44)
Symptomatology (%)	
Fever	95
Lymphadenopathy	75
Pharyngitis	70
Fatigue	50
Rash	70
Gastrointestinal symptoms	60
Headache	40
Myalgia/arthralgia	25
Oral thrush	25
Aseptic meningitis	25
Hepatosplenomegaly	20
Neuropathy	10
Genital ulcer	5
Meningoencephalitis	5
Oral ulcers	0
Laboratory abnormality (%)	
Leukopenia	35
Thrombocytopenia	35
Elevated aminotransferase levels	50
Baseline CD4+ and CD8+ lymphocyte counts (cells/μL) [median (range)]	
CD4+	312 (112-520)
CD8+	1300 (105-2540)
Baseline plasma viral load (copies/mL) [median (range)]	230,500 (602->750,000)

Table 2. Summary of drug resistance mutations in 11 isolates of patients with primary human immunodeficiency virus infection

Drug class	Mutation	Number
Nucleoside reverse transcriptase inhibitor	Any primary or secondary mutation	0
Non-nucleoside reverse transcriptase inhibitor	Any primary or secondary mutation	0
Protease inhibitor	Any primary mutations	0
	Any secondary mutation	9
	PR L10IRV	4
	PR M36I	3
	PR L63P	9
	PR A71VT	2
	PR V77I	6

Fever (95%) was the most common symptom followed by lymphadenopathy (75%), pharyngitis (70%), skin rashes (70%), and gastrointestinal symptoms (60%) including nausea, vomiting, and diarrhea. Fatigue (50%), headache (40%), myalgia and/or arthralgia (25%), and oral thrush (25%) were also common (Table 1). The neurologic presentations of acute retroviral syndrome were not uncommon and diverse. One patient presented with meningoencephalitis, 5 with aseptic meningitis, 1 with Guillain-Barré syndrome, and 1 with leg numbness. Of note was a case of amebic liver abscess and colitis as the initial presentation of primary HIV infection. The median duration of symptoms was 18.5 days (range, 5 to 44 days). Most patients had never sought medical help for the symptoms at emergency room (14 patients, 70%) or outpatient department (70%); 12 patients (60%) were hospitalized.

Thrombocytopenia (35%), leukopenia (35%), and elevated liver function test (LFT) [50%] were the most common findings in the laboratory tests. Hemophagocytosis observed in pathology of the bone marrow biopsy was noted in 2 patients with definite primary HIV infection. The initial median CD4+ count was 312 cells/μL (range, 112-520 cells/μL), CD8+ 1300 cells/μL (range, 105-2540 cells/μL), and the initial median plasma HIV RNA load was 230,500 RNA copies/mL (range, 602->750,000 copies/mL).

Highly active antiretroviral therapy (HAART) was begun in 13 patients (65%) with a median interval of 63 days (range, 7-752 days) from diagnosis of primary HIV infection to treatment initiation. The median follow-up duration after HAART was 770 days (range, 12-2223 days), with 1 patient lost to follow-up. Immunologic and virologic responses after initiation of HAART were analyzed in 11 patients. After the median treatment duration of 802 days (range, 233-2194 days), the median increase of CD4+ count was 287 cells/μL (range, 46-429 cells/μL), and the median decrease of CD8+ count 180 cells/μL (range, –711-1701 cells/μL). Virological failure developed in 2 patients while the other 9 patients achieved sustained viral suppression.

The course of CD4+, CD8+ count, and PVL changes without HAART was observed in 7 patients with a median follow-up duration of 359 days (range, 111-752 days). The median CD4+ change is 119 cells/mL (range, –230-352 cells/μL), median CD8+ change –110 cells/μL (range, –1185-536 cells/μL), and median change in plasma HIV RNA load $-\log_{10}$ 5.25 copies/mL (range, $-\log_{10}$ 5.86-$\log_{10}$ 5.38 copies/mL).

Of the 11 viral isolates subjected to phylogenetic tree analysis, 10 were classified as subtype B. The other was subtype CRF07-BC, which has caused serious AIDS epidemics in Mainland China. The genotypic resistance assay was performed on the same 11 isolates. Among these isolates, 2 isolates showed no mutations at any of the drug-resistant sites. For the remaining 9 isolates, no primary drug-resistant mutations were observed, although some secondary mutations on the protease gene were identified. The summary of mutation sites is listed in Table 2. Of the secondary mutations, the appearance of L63P and V77I are most frequent, with 9 and 6 out of the 9 specimens exhibiting such mutations. Whether these mutations represent drug resistance mutations or merely sequence characteristics of native HIV-1 strains in Taiwan requires further analysis.

Discussion

The first description of acute HIV infection was published in 1985 as a mononucleosis-like illness [10]. Although the symptomatic infection may be present in 40 to 90% of the patients [3], primary HIV infection is often underdiagnosed due to its asymptomatic presentations or nonspecific symptoms and signs, which may make it difficult for health care providers to

differentiate HIV from other acute virus infections. The acute retroviral syndrome may consist of skin rashes, mononucleosis-like illness with fever, lymphadenopathy, pharyngitis, and neurologic symptoms of aseptic meningitis, meningoencephalitis, and Guillain-Barré syndrome [11-13]. In this study, we found the clinical manifestations of primary HIV infection in Taiwanese patients to be similar to those of previous reports [11-13]. Of note were 2 diseases associated with primary HIV infection in our patients, which were rarely described before: amebic liver abscess and colitis and hemophagocytosis.

The interval from HIV exposure to the development of symptoms is usually 2 to 4 weeks, although incubation periods as long as 10 months have been described [14]. The acute illness may last from a few days to more than 10 weeks, but the duration is usually less than 14 days [11].

Schacker et al reported most (86-94%) patients with primary HIV infection had symptoms and sought medical help, and some (7-29%) even needed hospitalization for their clinical presentations [11]. In our study, 14 (70%) patients visited the emergency room, and 12 (60%) patients were admitted for the symptoms. Most (85%) of the cases in this study were diagnosed after 2000, suggesting the increasing recognition of primary HIV infection in these years. However, with the rapidly increasing rate of case numbers of HIV infection in Taiwan [2], health care providers should have a higher index of suspicion of primary HIV infection in patients at risk who present with a compatible clinical syndrome at the outpatient department or in the emergency room.

Patients with primary HIV infection may be highly infectious because of the presence of an enormous viral burden in blood and genital secretions [4], and many patients with primary HIV infection may not be aware of their disease and continue to practice risky sexual activities or needle-sharing. According to the report by Jacquez et al, a substantial proportion of HIV infections may have been transmitted by individuals with primary HIV infection [15]. From the public health perspective, it is therefore important to make an early diagnosis of primary HIV infection in order to provide timely counseling and education to prevent further transmission of HIV.

Whether or when to treat patients with primary HIV infection is still an area of uncertainty. There are only limited clinical trials supporting a beneficial effect on laboratory markers of disease progression with combination therapy [16-18]. DHHS recommends that patients and health care providers be made fully aware of the potential benefits and risks before considering initiation of antiretroviral therapy. The advantages of early intervention may include decreased severity of acute disease, alteration of the initial viral setpoint, reduction of the rate of viral mutation as a result of suppression of viral replication, preservation of immune function, and reduction of the risk for viral transmission. The potential disadvantages, however, are the adverse effects on quality of life resulting from drug toxicities and dosing constraints, drug resistance if therapy fails to effectively suppress viral replication, which might limit future treatment options, and a need to continue therapy indefinitely [19].

An increasing incidence of both high-level single drug and multidrug resistance has been observed in patients with primary HIV infection enrolled in 1999 to 2000 compared with 1995 to 1998: 12.4% vs 3.4% and 6.2% vs 1.1%, respectively [7]. There are currently no data regarding the resistant mutations of patients with primary HIV infection in Taiwan. Although no major resistance mutations were identified in a small number of viral isolates in this study, HIV may mutate under conditions of inadequate drug levels when patients have poor compliance or poor gastrointestinal absorption, which may limit future options of antiretroviral therapy or promote transmission of resistant virus. Because HIV-infected patients have free access to antiretroviral therapy since the introduction of protease inhibitors in April 1997 and non-nucleoside reverse transcriptase inhibitors in mid-1999 in Taiwan, education and counseling on adherence to antiretroviral therapy should be constantly reinforced while they are receiving therapy.

Over the past 20 years, the case number of HIV infection has increased at a staggering rate. In view of this situation, concerted efforts are required to stop the transmission of HIV in Taiwan, involving public education on safe sexual behaviors, early recognition of primary HIV by the medical community, and timely initiation of antiretroviral therapy in HIV-infected patients.

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