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Original Article

Primary Human Immunodeficiency Virus Infection Presenting as Elevated Aminotransferases

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BACKGROUND/PURPOSE: Primary human immunodeficiency virus type 1 (HIV-1) infection is often under-diagnosed because of its nonspecific presentations. Elevated aminotransferase levels is one of its clinical manifestations, but is infrequently reported in the literature. The objective of this study was to investigate cases of elevated aminotransferases as a manifestation of primary HIV-1 infection.
METHODS: A retrospective chart review from October 1990 to May 2009 of HIV-1 infected patients in a registered database at a tertiary hospital was conducted to identify patients diagnosed with primary HIV-1 infection. An elevated aminotransferase level was broadly defined as above-normal values of alanine or aspartate aminotransferases. Acute hepatitis markers were determined using stored serum samples.
RESULTS: Twenty-three of the 827 (2.8%) patients were identified as having a primary HIV-1 infection. All were male, with a median age of 26 years (range, 19–77 years), and the majority were men who had sex with men (19/23, 82.6%). The most common clinical manifestations were fever (95.7%), elevated aminotransferases (65.2%), fatigue (47.8%), and pharyngitis (47.8%). The median CD4 lymphocyte count was 374/μL (range, 109–674/μL) and the median log HIV viral load was 5.0 (range, 4.3–5.9). For the 15 patients with abnormal liver function tests, the median aspartate aminotransferase level was 112 U/L (range, 62–969 U/L) and the median alanine aminotransferase level was 146 U/L (range, 42–1,110 U/L).
CONCLUSION: Elevated aminotransferases may be an initial manifestation of primary HIV infection and is more common than expected. Primary HIV-1 infection should be one of the differential diagnoses considered in young men presenting with unexplained, new-onset liver function impairment.

KEYWORDS: acute HIV-1 infection, acute retroviral syndrome, hepatitis, primary HIV-1 infection

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Introduction

Primary human immunodeficiency virus type-1 (HIV-1) infection has a broad clinical spectrum ranging from asymptomatic seroconversion to symptomatic mononucleosis-like syndrome, which is also referred to as acute HIV-1 infection, or acute retroviral syndrome. According to the literature, the incidence of symptomatic illness ranges from 40% to 90%,[1] and usually presents within 2–6 weeks after exposure and resolves within 1–2 weeks.[2] The most common manifestations include fever, fatigue, rashes (usually maculopapular), headache, lymphadenopathy, pharyngitis, myalgia, arthralgia, aseptic meningitis, retro-orbital pain, weight loss, depression, gastrointestinal distress, night sweats, and oral or genital ulcers.[1–4] During this period, the infected individual often has a very high viral load but maintains high-risk behavior, such as unprotected sex and intravenous drug use with shared needles. From a public health point of view, early recognition and diagnosis of primary HIV-1 syndrome provides not only an opportunity for early treatment, but also for interruption of HIV-1 transmission.

Elevated aminotransferases is one of the characteristics of primary HIV-1 infection, or acute retroviral syndrome, with a frequency of 21% reported in the literature.[1,3,4] In a case study from the National Taiwan University Hospital, 10/20 patients (50%) had elevated hepatic enzymes.[5] Case reports from the Cheng-Kung University Hospital found all three cases of primary HIV-1 infection to have elevated aminotransferases.[6]

Based on our clinical experience, elevated aminotransferases occur rather frequently in patients with primary HIV-1 infection. Our study aims to describe the clinical manifestations of primary HIV-1 infection in a tertiary hospital, to determine the frequency and to elucidate the possible causes of elevated liver enzymes in patients with primary HIV-1 infection.

Methods

Study subjects

A retrospective chart review of all patients diagnosed with HIV-1 infection in a registered database was conducted at Kaohsiung Veterans General Hospital, a tertiary hospital in Southern Taiwan, from October 1990 to May 2009, to identify subjects with primary HIV-1 infection. This included any of the following: (1) Patients clinically diagnosed as primary HIV-1 infection based on recent high-risk behavior, relatively high viral loads and normal CD4 counts, and compatible retroviral symptoms 3 months before serological positivity; (2) a positive enzyme immunoassay test for HIV-1 with indeterminate Western blot results (World Health Organization criteria), and two separate positive results for reverse transcriptase-polymerase chain reaction; or (3) negative serologic tests 6 months prior to symptoms compatible with primary HIV-1 infection, with positive HIV enzyme-linked immuno sorbent assay and Western blot results.[7] The HIV-1 viral load was assessed using the Roche Cobas Amplicor HIV-1 monitor test (version 1.5) (Roche Branchburg, NJ, USA) and CD4 count was done using the Beckman Coulter Cyto-stat/Coulter Clone (Beckman Coulter, Fullerton, CA, USA).

Elevated aminotransferases was broadly defined as values of either alanine aminotransferase or aspartate aminotransferase above the upper normal limit. Acute hepatitis markers, including immunoglobulin M to hepatitis A virus (HAV-IgM), hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV) antibody, antibody to early antigen of Epstein-Barr virus, immunoglobulin M to cytomegalovirus (CMV-IgM), and immunoglobulin G to cytomegalovirus (CMV-IgG) were also checked when stored serum or plasma samples were available.

Results

From October 1990 to May 2009, 23 patients with acute HIV-1 infection were identified after reviewing 827 HIV-1 positive patients. All were male, with a median age of 26 years (range, 19–77 years). The median CD4 count was 374/μL (range, 109–674/μL) and the median log HIV-1 viral load was 5.0 (range, 4.3–5.9). The major risk factors for HIV-1 infection were MSM (men who have sex with men; 82.6%) and heterosexual sex (13.1%). None were intravenous drug users. The most common clinical manifestations were fever (95.7%), elevated aminotransferases (65.2%), fatigue (47.8%), pharyngitis (47.8%), skin rashes (43.5%), and gastrointestinal symptoms (39.1%) (Table 1).

About two-thirds of the patients (15/23; 65.2%) had elevated aminotransferases, and 12/15 patients (80.0%) had serum or plasma samples available for further analysis.

Table 1. Demographic data and clinical manifestations of patients with primary HIV-1 infection[a] ($n=23$)

Characteristics	
Age (yr)	26 (19–77)
Gender, male	23 (100)
CD4 count (/μL)	374 (109–674)
CD8 count (/μL)	989 (190–2,168)
Log_{10} HIV viral load (copies/mL)	5.0 (4.3–5.9)
Route of HIV transmission	
Men who have sex with men	19 (82.6)
Heterosexual	3 (13.1)
Unknown	1 (4.3)
Clinical manifestations (%)	
Fever	95.7
Elevated aminotransferases	65.2
Fatigue	47.8
Pharyngitis	47.8
Skin rash	43.5
Gastrointestinal symptoms	39.1
Lymphadenopathy	34.8
Leukopenia	30.4
Thrombocytopenia	30.4
Headache	21.7
Myalgia	21.7
Aseptic meningitis	17.4
Hepatosplenomegaly	13.0
Oral thrush	8.7

[a]Data presented as median (range) or *n* (%) or %.

Table 2. Biochemistry of patients with primary HIV-1 infection ($n=15$)

Biochemistry	Median (range)
AST (U/L)	112 (62–969)
ALT (U/L)	146 (42–1,110)
Total bilirubin (mg/dL)	0.8 (0.3–3.0)

AST=Aspartate amino transferases; ALT=alanine amino transferases.

Table 3. Acute hepatitis markers of patients with primary HIV-1 infection

Hepatitis marker positivity	First serum ($n=12$)	Paired serum ($n=6$)
HAV-IgM	0 (0)	0 (0)
HBsAg	0 (0)	0 (0)
Anti-HCV Ab	0 (0)	0 (0)
EBV-EA Ab	0 (0)	0 (0)
CMV-IgM[a]	3 (25.0)	NA
VDRL positive[b]	4 (33.3)	NA

[a]CMV IgM antibody: 1.42, 3.49 and 4.35 (cutoff=0.8–1.1). All cases had a positive CMV-IgG titer. [b]VDRL titers: 1:32, 1:16, 1:4, 1:2. HAV-IgM=Immunoglobulin M to hepatitis A virus; HBsAg=hepatitis B surface antigen; anti-HCV Ab=anti-hepatitis C virus antibody; EBV-EA Ab=antibody against early antigen of Epstein–Barr virus; CMV-IgM=immunoglobulin M to cytomegalovirus; VDRL=Venereal Disease Research Laboratory; NA=not available.

Moreover, 6/15 patients (40.0%) had a paired serum sample taken 6 months later (Tables 2 and 3). All those tested were negative for HAV-IgM, HBsAg, and anti-HCV antibody. Antibody to early antigen of Epstein-Barr virus was negative in the first serum samples. Three cases were positive for IgM to CMV at low titer (1.42, 3.49 and 4.35, respectively; cutoff=0.8–1.1) and all were concomitantly positive for IgG to CMV. Aside from viruses, 4/15 (26.6%) had a positive Venereal Disease Research Laboratory test, with titers of 1:32, 1:16, 1:4, and 1:2, respectively.

Discussion

Primary HIV-1 infection was first reported in 1985 as a mononucleosis-like illness.[3] Although 40–90% of patients present symptomatically, this syndrome is often underdiagnosed because of its nonspecific presentations.[1] In a group of 23 people at risk of HIV-1 infection involved in routine surveillance programs with HIV-1 testing every 6 months, 87% had symptomatic acute infection and 95% sought medical evaluation. Even with a high index of suspicion, only one-fourth were correctly diagnosed with primary HIV-1 infections on their first visit.[7] Because of nonspecific presenting symptoms and signs, primary HIV-1 infection is frequently confused with a variety of other illnesses, such as infectious mononucleosis, secondary syphilis, acute hepatitis A or B, and other viral infections. Therefore, most of the literature related to primary HIV-1 infection focuses less on clinical symptoms, but more on diagnosis or prognostic impact (Table 4). In our study, 23/827 (2.8%) HIV-1 positive patients were identified as having a primary HIV-1 infection. The reasons for such a low rate included the confusing symptoms of primary HIV-1 infection, clinical

Table 4. Clinical symptoms and signs during primary HIV infection

	Niu et al[2]	HY Sun et al[4]	ST Huang et al[5]	Schacker et al[7]
Sample size (*n*)	209	20	3	46
Sex, M/F	–	20/0	3/0	43/3
Median age (yr)	–	31	24	30
MSM transmission[a]	–	18 (90)	2 (67)	42 (91)
Top 3 symptoms/signs	Fever (96%) Adenopathy (74%) Pharyngitis (70%) Rash (70%)	Fever (95%) Lymphadenopathy (75%) Pharyngitis (70%) Rash (70%)	–	Fever (93%) Fatigue (89%) Pharyngitis (70%)
Abnormal liver function tests (%)	21	50	100	–

[a]Data presented as *n* (%).

inattention of first-line clinicians, and poor serology detection tools for primary HIV-1 infection.

In the literature, abnormal liver function tests were seen in up to 21% of patients with primary HIV-1 infection.[1,3,4] However, the nature of the association between primary HIV-1 infection and hepatitis has not been described. The first case of acute hepatitis associated with primary HIV-1 infection was reported in 1992. The report described a young woman originating from Ghana who had an unexplained fever with abdominal pain and abnormal liver function tests. Despite intensive evaluation of hepatitis markers and even exploratory laparotomy, all of the results were negative. The symptoms spontaneously resolved after 1 week. Two years later, she was diagnosed with HIV-1 infection presenting with an opportunistic infection. The original serum sample taken 2 years previously was retrospectively tested and was found to be positive for HIV-1.[8]

There have only been two reports describing the association between elevated aminotransferases and primary HIV-1 infection in Taiwan. In a case study from the National Taiwan University Hospital, 10/20 of HIV-1 infected patients (50%) had elevated hepatic enzymes.[5] Another case study from the Cheng-Kung University Hospital reported three cases of primary HIV-1 infection, all of which had elevated aminotransferases.

Taiwan is a hyperendemic area for viral hepatitis, with HBV and HCV seroprevalences of 17.3% and 4.4%, respectively.[9] It is therefore necessary to screen the status of viral hepatitis in patients with naïve HIV-1 infection on their first visit, even those with initially normal liver function tests, and normal antibody levels to hepatitis A, HBsAg, surface and anti-core antibodies of hepatitis B, and anti-hepatitis C. Patients with elevated aminotransferases should be further tested for HAV-IgM and HBV core IgM, and for viral loads of HCV.

In the current case study, elevated aminotransferases was the second most common clinical presentation, and present in two-thirds of patients, although none were seropositive for HAV-IgM, HBsAg, and anti-HCV antibody. Three cases had low titer positivity for anti-CMV IgM, but the presence of this antibody in a single serum sample is insufficient for the diagnosis of a current primary infection. The reasons include: (1) IgM antibodies can persist for months after a primary infection, or reappear during recurrences;[10] (2) a heterotypical immune response caused by inter-current infections;[11] and (3) possible reactivation of a latent viral infection due to transient suppression of cellular immune functions.[12] Because all three cases also had antibodies to CMV (IgM and IgG), the elevated hepatic enzymes were less likely to be attributable to CMV infection.

Other than viruses, *Treponema pallidum*, the cause of syphilis, is known to cause diseases in every organ in the human body, including the liver. One case study reported seven cases of syphilitic hepatitis in HIV-1 infected patients, with a conspicuous increase in serum alkaline phosphatase level that resolved rapidly after effective antibiotic

treatment.[13] In the current case study, four cases with elevated aminotransferases also had a positive Venereal Disease Research Laboratory test. Three were tested for alkaline phosphatase, and all were within the normal range. One patient had previously been treated for syphilis and did not show any symptoms associated with syphilis. Only one patient underwent lumbar puncture to exclude neurosyphilis and received a standard 3-week penicillin treatment.

Because of the nonspecific presentation of primary HIV-1 infection and the relatively few clinical cases, this study has some limitations. First, it is a retrospective study, so the history of concurrent medications may be unreliable. Second, for those who met criterion one and were diagnosed with primary HIV-1 infection, the detuned test was not available to determine the timing of infection. Third, hepatitis was broadly defined as elevated hepatic aminotransferases and not based on histopathologic findings. Nevertheless, invasive diagnosis using a liver biopsy for elevated aminotransferases that resolve spontaneously is not feasible in the clinical setting. Finally, serum samples were not available for further detailed tests, such as hepatitis C viral load or serial changes in serology titers. However, our study highlights the association between elevated aminotransferases and primary HIV-1 infection, and further prospective studies will allow more fully clarification of the nature of this association.

In conclusion, elevated aminotransferases may be one of the initial manifestations of primary HIV-1 infection and is probably more common than expected. Abnormal liver function tests may be related to HIV-1 infection, or to other concomitant viral or syphilitic hepatitis. Physicians should have a high index of suspicion for the possibility of primary HIV-1 infection when treating young males who present with unexplained, recent-onset liver function impairment. Aside from testing for other hepatotropic viruses, such as hepatitis A, B and C, detailed risk stratification of unprotected sex or intravenous drug use, and serological tests for HIV-1, should be conducted to enable diagnosis of primary HIV-1 infection, earlier management, and interruption of transmission.

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