J Microbiol Immunol Infect.
2008;41:456-461

Original Article

Comparison of clinical characteristics of amebic liver abscess in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients

Kuan-Sheng Wu[1], Hung-Chin Tsai[1], Susan Shin-Jung Lee[1], Yung-Ching Liu[1,2], Shue-Ren Wann[1], Yung-Hsing Wang[1], Ming-Hsin Mai[1], Jei-Kuang Chen[1], Cheng-Len Sy[1], Kung-Ming Chen[1], Yi-Jan Chen[1], Yao-Shen Chen[1]

[1]Section of Infectious Diseases, Department of Medicine, and [2]Section of Microbiology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Received: July 2, 2007 Revised: July 24, 2007 Accepted: August 31, 2007

Background and Purpose: Amebic liver abscess is an emerging parasitic disease in human immunodeficiency virus (HIV)-infected patients. Clinical characteristics of this disease have rarely been compared between patients with and without HIV infection.

Methods: This retrospective study included 24 patients who had been diagnosed with amebic liver abscess during a 17-year period. The demographics, clinical manifestations, radiographic findings, and outcomes were compared between HIV-infected and non-HIV-infected patients.

Results: Among 24 patients with amebic abscess, 8 were HIV-infected and 16 were non-HIV-infected. The mean (± standard deviation [SD]) age of HIV-infected patients was 41.0 ± 11.3 years (range, 27-62 years), which was younger than that of the non-HIV-infected group (58.5 ± 14.6 years; range, 27-77 years; p=0.01). Compared with non-HIV-infected controls, patients with HIV infection had lower white blood cell counts (median, 17.2 × 10^9/L vs 10.4 × 10^9/L; p=0.01), neutrophil/lymphocyte (N/L) ratio (median, 12.1 vs 2.7; p<0.01), total bilirubin (median, 42.7 μmol/L vs 13.7 μmol/L; p=0.02), blood urea nitrogen (median, 7.9 mmol/L vs 4.1 mmol/L; p=0.04), and creatinine (median, 114.9 μmol/L vs 88.4 μmol/L; p<0.01). On multivariate analysis, low N/L ratio remained a significant predictor for HIV infection (odds ratio, 0.49; 95% confidence interval, 0.264-0.912; p=0.024). No significant differences were observed in clinical manifestations, radiographic findings, and indirect hemagglutination titer between the 2 groups.

Conclusion: HIV-infected patients with amebic liver abscess tended to have a lower N/L ratio than non-HIV-infected comparators.

Key words: *Entamoeba histolytica*; HIV infections; Liver abscess, amebic; Taiwan

Introduction

Invasive amebiasis, caused by *Entamoeba histolytica*, remains the second leading cause of death from parasitic diseases in the world [1]. Geographic differences exist in the distribution of *E. histolytica* in patients with human immunodeficiency virus (HIV)-infection. In the Asia-Pacific area, higher seroprevalence and gastrointestinal tract colonization of *E. histolytica* were identified in HIV-infected patients [2,3], which might explain why invasive amebiasis presented as an emerging disease among this group of patients [4,5]. In contrast, western countries have far lower prevalence figures for amebic infection and fewer invasive amebiasis cases [6]. Despite these discrepancies, HIV-infected patients with invasive amebiasis are predominantly men who have sex with men (MSM) and often have a relatively high CD4 count at diagnosis with invasive amebiasis [3].

Amebic liver abscess is the most common form of extraintestinal invasive amebiasis. Clinical characteristics

Corresponding author: Dr. Yao-Shen Chen, Section of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung 81346, Taiwan.
E-mail: yschen@vghks.gov.tw

of amebic liver abscess in non-HIV-infected patients are well understood [1,7-10]. However, comparison of clinical characteristics of amebic liver abscess between HIV-infected patients and non-HIV-infected controls has rarely been reported [11]. This retrospective study was conducted to compare the demographics, clinical manifestations, radiographic findings, and outcomes between these 2 groups of patients.

Methods

Patients

All medical records of patients who had been diagnosed with amebic liver abscess at Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, a tertiary medical center in southern Taiwan, from October 1990 to July 2007 were reviewed. A patient was diagnosed as having definite amebic liver abscess if the liver abscess aspirate was demonstrated to have trophozoites of *Entamoeba* under microscopic examination. If a patient fulfilled all the criteria listed below without demonstration of trophozoites of *Entamoeba* in the liver abscess aspirate, the diagnosis was considered to be probable amebic liver abscess:

- clinical symptoms of liver abscess, such as fever, chills, or abdominal pain;
- radiological findings of liver abscess, either by ultrasonography or computed tomography;
- serum indirect hemagglutination (IHA) assay for *E. histolytica* revealed a titer ≥1:128; and
- negative bacterial culture of blood and liver abscess aspirate, and a clinical response to metronidazole treatment.

The demographics, clinical manifestations, roentgenographic findings, laboratory data, treatment, and outcome of these patients were collected and analyzed.

Definitions

In all cases, HIV infection was confirmed by the Western blot method, and the acquired immunodeficiency syndrome (AIDS) definition was based on the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults [12]. Patients who had drunk untreated water 1 month prior to onset of clinical symptoms were considered to have a recent untreated water intake history. Abscess size (maximal diameter), was calculated only in patients with a solitary abscess. Time to defervescence indicated the interval from the time of giving metronidazole at an appropriate dose and interval to the time the patient's body temperature decreased to below 37.0°C. All laboratory data, except amebic IHA titer, were collected on the first day of admission to hospital. IHA assays were conducted following the manufacturer's instructions (Dade Behring Inc., Newark, DE, USA). Complications of amebic liver abscess included rupture of the abscess into the peritoneal cavity, or the right side empyema proved by visible trophozoites in pleural fluid.

Statistical analysis

For the univariate analysis, categorical variables were compared using Fisher's exact test, and continuous variables using Mann-Whitney *U* test. The result was considered to be significant if the 2-tailed *p* value was less than 0.05. Multivariate analysis using logistic regression with the forward stepwise method was then performed for those variables with significant differences at univariate analysis. A *p* value less than 0.05 was used as an inclusion criterion and a value of 0.1 was used as a removal criterion. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS, Chicago, IL, USA).

Results

Twenty four patients were diagnosed with amebic liver abscess in this 17-year retrospective study, including 6 definite and 18 probable cases (Fig. 1). Male gender predominated (n = 20, 83.3%). The mean age of these patients was 52.7 ± 15.8 years, with a range of 27 to 77 years. Only 1 patient (4.2%) had diabetes mellitus and 4 (16.7%) had recent untreated water intake history. The most common symptom at presentation was fever (n = 24, 100%), followed by abdominal pain (n = 18, 75.0%) and chills (n = 16, 66.7%) [Table 1]. Up to 58.3% of patients (n = 14) had an abnormal chest radiograph, which might suggest a liver parenchymal disease on admission, such as right side pleural effusion (n = 6), right hemidiaphragm elevation (n = 5), or increased pulmonary infiltrates over the right lower lung (n = 3). All patients underwent either abdominal ultrasonography or computed tomography examination. The liver abscess was located in the right hepatic lobe in 19 patients (79.2%). Liver abscess aspirates were obtained from 23 patients and all of them underwent microscopic examination and bacterial culture. Trophozoites were identified in 6 liver abscess aspirates under microscopic examination.

Eight patients were HIV-infected; 4 acquired the infection by heterosexual routes, 3 were MSM, and no

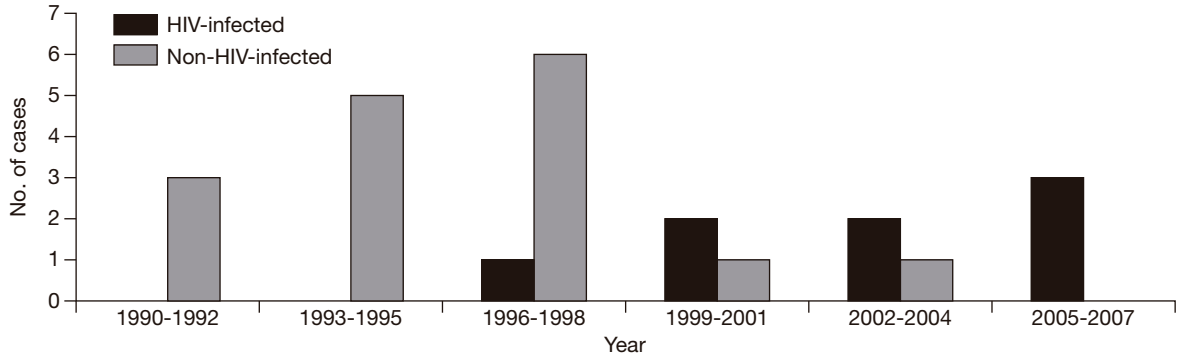

Fig. 1. Distribution of patients with amebic liver abscess according to admission year and human immunodeficiency virus (HIV) status.

certain risk factor could be identified for the remaining patient. HIV-infected patients tended to have amebic liver abscess at a younger age than the comparators (mean, 41.0 ± 11.3 years [range, 27-62 years] vs 58.5 ± 14.6 years [range, 27-77 years]; p=0.01). The mean CD4 count for HIV-infected patients was 465 ± 242 cells/μL (range, 219-919 cells/μL). Three patients were newly diagnosed with HIV infection while 2 had already received antiretroviral therapy. Three patients had concomitant opportunistic infection when diagnosed with amebic liver abscess: 1 each had salmonellosis, oral candidiasis, and oral hairy leukoplakia.

Comparing HIV-infected and HIV-non-infected patients, there was no difference in symptom duration before admission (mean, 7.0 ± 2.6 and 9.6 ± 9.1 days, respectively; p=0.65), duration to metronidazole treatment (mean, 8.4 ± 2.3 and 10.7 ± 8.6 days, respectively; p=0.58), symptoms and signs, abscess size (mean, 6.7 ± 3.1 and 8.1 ± 1.8 cm, respectively; p=0.42), abscess location, and amebic IHA titer. However, compared with non-HIV-infected patients, HIV-infected patients had higher lymphocyte count percentage (p<0.001), but had lower white blood cell count (p=0.01), neutrophil/lymphocyte (N/L) ratio (p<0.001), neutrophil count percentage (p<0.01), total bilirubin (p=0.02), blood urea nitrogen (p=0.04) and creatinine (p<0.01) [Table 2]. Low N/L ratio remained a significant predictor for HIV infection when controlled for age, total bilirubin, and creatinine (odds ratio, 0.49; 95% confidence interval, 0.264-0.912; p=0.024).

IHA assay for *E. histolytica* was collected for all patients. Using 1:128 or greater as a cut-off value, 22 patients had an elevated IHA titer. Sensitivity of IHA titer for diagnosing amebic liver abscess was 91.7%.

Table 1. Demographics and clinical manifestations of amebic liver abscess in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients

Variable	HIV-infected patients (n = 8) No. (%)	Non-HIV-infected patients (n = 16) No. (%)	All patients (n = 24) No. (%)	p
Age (years; mean [SD])	41.0 (11.3)	58.5 (14.6)	52.7 (15.8)	0.01[b]
Males	8 (100.0)	12 (75.0)	20 (83.3)	0.26
Time to treatment (days; mean [SD])[a]	8.4 (2.3)	10.7 (8.6)	9.9 (7.0)	0.58
Symptoms				
Fever	8 (100.0)	16 (100.0)	24 (100.0)	1.00
Abdominal pain	8 (100.0)	10 (62.5)	18 (75.0)	0.07
Chills	6 (75.0)	10 (62.5)	16 (66.7)	0.67
Diarrhea	4 (50.0)	3 (18.8)	7 (29.2)	0.17
Respiratory tract symptoms	1 (12.5)	3 (18.8)	4 (16.7)	1.00
Nausea/vomiting	0 (0)	4 (25.0)	4 (16.7)	0.26
Malaise	1 (12.5)	2 (12.5)	3 (12.5)	1.00
Weight loss	1 (12.5)	1 (6.25)	2 (8.3)	1.00

Abbreviation: SD = standard deviation

[a]Time from symptom onset to metronidazole treatment.

[b]p Value was statistically significant.

Table 2. Radiographic findings and laboratory data of amebic liver abscess in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients

Variable	HIV-infected patients (n = 8) No. (%)	Non-HIV-infected patients (n = 16) No. (%)	All patients (n = 24) No. (%)	*p*
Radiographic findings				
Solitary abscess	5.0 (62.5)	15.0 (93.8)	20.0 (83.3)	
Abscess size (cm; mean [SD])[a]	6.7 (3.1)	8.1 (1.8)	7.6 (2.4)	0.42
Right hepatic lobe	4 (50.0)	15 (93.8)	19 (79.2)	
Amebic IHA titer				
<128	0 (0)	2 (12.5)	2 (8.3)	
128-512	2 (25.0)	4 (25)	6 (25)	
≥1024	6 (75.0)	10 (62.5)	16 (66.7)	
Laboratory data (median) [IQR]				
White blood cell count ($\times 10^9$/L)	10.4 (3.1)	17.2 (7.6)	14.9 (7.1)	0.01[b]
Hemoglobin (g/L)	110 (12)	120 (19)	117 (17)	0.07
Platelets ($\times 10^9$/L)	276.1 (114.4)	249.4 (111.4)	257.6 (110.4)	0.34
Neutrophil percentage	65.0 (15.1)	84.0 (4.5)	77.4 (13.1)	<0.01[b]
Lymphocyte percentage	26.3 (10.1)	7.5 (3.6)	13.5 (10.9)	<0.001[b]
Monocyte percentage	8.0 (3.9)	5.6 (3.0)	6.4 (3.4)	0.20
Eosinophil percentage	3.3 (0.8)	0.8 (1.1)	1.6 (2.9)	0.11
N/L ratio	2.7 (4.2)	12.1 (9.3)	8.7 (10.3)	<0.001[b]
AST (U/L)	43.5 (21.0)	81.5 (55.1)	68.8 (49.5)	0.13
ALT (U/L)	43.0 (28.8)	66.8 (51.8)	58.8 (46.2)	0.34
Total bilirubin (μmol/L)	13.7 (6.8)	42.7 (35.9)	32.5 (32.5)	0.02[b]
ALP (U/L)	219.1 (125.2)	215.6 (227.0)	216.8 (195.5)	0.55
Albumin (g/L)	27 (6)	26 (5)	26 (5)	0.49
Blood urea nitrogen (mmol/L)	4.1 (2.0)	7.9 (5.7)	6.6 (5.0)	0.04[b]
Creatinine (μmol/L)	88.4 (17.7)	114.9 (35.4)	106.1 (35.4)	<0.01[b]
Sodium (mmol/L)	137.5 (3.4)	133.4 (7.8)	134.8 (6.9)	0.24
Potassium (mmol/L)	4.2 (0.7)	3.7 (0.6)	3.8 (0.7)	0.13

Abbreviations: SD = standard deviation; IHA = indirect hemagglutination; IQR = interquartile range; N/L ratio = neutrophil/lymphocyte ratio; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

[a]Only solitary abscesses were included.

[b]*p* Value was statistically significant.

Two patients without IHA titer elevation were both non-HIV-infected and had a recent untreated water intake history. One of them underwent repeat IHA titer examination 2 weeks after treatment and still had a low IHA titer. IHA titer did not significantly correlate with abscess size (Spearman's rho correlation coefficient, –0.086; p=0.78), time to defervescence (Spearman's rho correlation coefficient, 0.03; p=0.90) or hospital stay (Spearman's rho correlation coefficient, –0.19; p=0.37).

All 24 patients received metronidazole 500 to 750 mg 3 times a day. Most of them (n = 23) had their abscess aspirated or drained. There were no complications owing to drainage or aspiration (such as fistula formation or bleeding). Among those who underwent drainage, HIV-infected patients had a shorter drainage time (3.8 vs 6.7 days; p=0.05). Four non-HIV-infected patients developed complications of amebic liver abscess (Table 3), 3 with ruptured abscess leading to peritonitis and 1 with right-side empyema. Time to defervescence was shorter in HIV-infected patients (45.2 vs 120.2 h; p=0.03), but the comparison did not reach statistical significance when controlled for age (p=0.10). There was no significant effect of HIV status on duration of metronidazole use, length of hospital stay, and complication rate. All patients survived without permanent sequelae.

Discussion

There are only a few reports of amebic liver abscess in HIV-infected patients in the literature [3,4,13,14], and comparative data on clinical characteristics of amebic liver abscess in HIV-infected and non-HIV-infected

Table 3. Treatment and outcomes of amebic liver abscess in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients

Variable	HIV-infected patients (n = 8) No. (%)	Non-HIV-infected patients (n = 16) No. (%)	All patients (n = 24) No. (%)	*p*
Treatment modality				
Medication only	0 (0)	1 (6.25)	1 (4.2)	
Medication and aspiration	2 (25)	4 (25)	6 (25)	
Medication and percutaneous drainage	6 (75)	10 (62.5)	16 (66.7)	
Medication and surgery	0 (0)	1 (6.25)	1 (4.2)	
Hospital course (days; median) [IQR]				
Drainage duration[a]	3.8 (3.1)	6.7 (4.2)	5.6 (4.0)	0.05[c]
Duration of metronidazole use	14.8 (4.7)	19.9 (7.0)	18.2 (6.7)	0.07
Time to defervescence (h)[b]	45.2 (56.9)	120.2 (73.7)	97.7 (76.2)	0.03[c]
Hospital stay	12.5 (3.6)	14.1 (4.4)	13.6 (4.1)	0.46
Complications	0 (0)	4 (25)	4 (16.7)	0.26

Abbreviation: IQR = interquartile range

[a]Only patients receiving percutaneous drainage were included.

[b]Time from giving metronidazole until body temperature decreased to below 37.0°C.

[c]*p* Value was statistically significant.

patients are rare. A previous retrospective study conducted in Thailand, which included 62 patients (23 HIV-infected and 39 non-HIV-infected) showed no significant difference in age, gender, duration of clinical presentation, and symptoms and signs between these 2 groups of patients [11]. In that study, radiographic findings, laboratory data, and hospital course were not compared [11].

Our study noted several differences in clinical characteristics associated with HIV patients, including a significantly lower N/L ratio. To the best of our knowledge, this finding has never been mentioned in the literature. In a large-scale study conducted in a metropolitan area in northern Taiwan, the seroprevalence of *E. histolytica* was only 0.1% in healthy people and 1.8% in patients with gastrointestinal symptoms, but up to 7.1% in HIV-infected patients [2]. This implies a low prevalence of *E. histolytica* infection in non-HIV-infected patients in Taiwan. From this result, we could further assume that in our study when non-HIV-infected patients developed an amebic liver abscess, it was likely to have been the first time that they had had the disease. Neutrophilic lymphocytosis would be more prominent in such an acute infection. HIV-infected patients might have already had asymptomatic amebiasis or *E. histolytica* intestinal colonization before the amebic liver abscess episode. Thus, the disease episode was more likely to have provided a 'booster' effect than an acute infection, leading to relatively less lymphocytosis. Thus, HIV-infected patients tended to have a lower N/L ratio. Further studies are needed to clarify this hypothesis.

Secondly, HIV-infected patients were younger than non-HIV-infected controls in this study, which was different from the result of a previous study [11]. Geographic differences might account for the differing risk factors for contracting amebic liver abscess. In developing countries with a high prevalence of amebic infection, people tend to contract amebic liver abscess via the oral-fecal route in the environment; the correlation of HIV infection and invasive amebiasis is relatively insignificant [15]. The demographic differences, including age and gender, between HIV-infected and non-HIV-infected patients would thus be minimized. However, in areas non-endemic for amebiasis, such as Taiwan, amebiasis in HIV-infected patients is most likely transmitted via high-risk behavior, such as unprotected oral-anal sex, rather than background environment transmission. In this situation, the demographics of amebic liver abscess between HIV-infected and non-HIV-infected patients would differ considerably. A previous study conducted in northern Taiwan also showed that persons with a high IHA titer of *E. histolytica* were younger in groups with HIV infection and at risk for HIV infection than in the non-HIV-infected population [2].

Finally, HIV-infected patients had a shorter time to defervescence (p=0.03), and lower total bilirubin (p=0.02), blood urea nitrogen (p=0.04), and creatinine (p<0.01) under univariate analysis. Although the

results for these variables were no more significant under multivariate analysis, there was a tendency for amebic liver abscess to have a milder clinical course in HIV-infected patients. This borderline significance could also be explained by the effect of prior exposure ('partial vaccination') in HIV-infected patients.

Most non-HIV-infected patients had amebic liver abscess in the first half of the 17-year study period, while in HIV-infected patients this occurred mostly in the second half (Fig. 1). Similar findings have been reported elsewhere [4,5]. This suggests that amebic liver abscess is indeed an emerging parasitic disease in patients with HIV infection. Moreover, HIV-infected patients tended to have a relatively high CD4 count when diagnosed with invasive amebiasis [3]. Thus, it is rational to check for HIV antibody in all patients with amebic liver abscess in areas with low background prevalence of amebiasis, such as Taiwan.

There are some limitations to this study. Firstly, owing to the retrospective nature of the study, not all patients in the non-HIV-infected group received HIV antibody test. In this situation, we assigned non-HIV-infected patients mainly based on history taking and physical examination. Secondly, due to the small sample size, the power of multivariate analysis was relatively low.

In conclusion, we noted some differing clinical characteristics of amebic liver abscess between HIV-infected and non-HIV-infected patients in Taiwan. HIV-infected subjects tended to have amebic liver abscess at a younger age, presented with a lower N/L ratio, and increased in number in recent years. There was no significant difference in symptoms and signs, radiographic findings, other laboratory data, and hospital course between these 2 groups of patients. Clinicians should be aware of the possibility of concomitant HIV infection when diagnosing amebic liver abscess in Taiwan.

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