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Original Article

Diagnostic Value of Percutaneous Liver Biopsy in Fever of Unkown Origin in Patients with Human Immunodeficiency Virus Infection

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SUMMARY: Fever of unknown origin (FUO) poses a major diagnostic challenge in patients infected with human immunodeficiency virus (HIV). In this retrospective study, we sought to assess the clinical utility of percutaneous liver biopsy as a diagnostic aid for FUO in HIV-infected patients and identify the factors associated with a greater likelihood of a positive diagnostic yield form this procedure. A total of 101 HIV-infected patients with FUO, who had undergone percutaneous liver biopsy in an HIV care hospital, served as the study population. The results obtained from percutaneous liver biopsy were categorized into three groups: (i) diagnostic, (ii) helpful, and (iii) not helpful. Diagnostic and helpful results were classified as useful. The mean (SD) age of patients was 37.6 (6.9) years, and the median (interquartile range [IQR]) CD4 count was 18 (3–62) cells/mm^3. The median (IQR) duration of fever was 20 (8–30) days. Percutaneous liver biopsy was diagnostic in 51 patients (50.5%), helpful in 12 (11.9%) and not helpful in 38 (37.6%) patients. On multivariate analyses, elevation of serum alkaline phosphatase level (OR 1.27 per one time elevation from the upper normal range; 95% CI, 1.03–1.57; $P = 0.023$), and fever duration of less than 3 weeks (OR 3.82; 95% CI, 1.03–14.18; $P = 0.046$) was significantly associated with the likelihood of the biopsy findings being classified as useful. Our study supports the case for percutaneous liver biopsy as a useful diagnostic aid in HIV-infected patients with FUO.

INTRODUCTION

Prolonged fever is a common presentation of human immunodeficiency virus (HIV)-infection in the early stage of the diseases (1). Fever of unknown origin (FUO) has also been acknowledged as a major issue among these patients (2–5). The advent of combined highly active antiretroviral therapy (HAART) has largely contributed to the declining morbidity and mortality rates among HIV-infected patients in both resource-rich and resource-constrained countries (6–8). Recent studies have demonstrated the linkage between reduced incidence of FUO in the HIV-infected patients and the wider availability and access the HAART (9,10). Nonetheless, FUO continues to be a problem in countries with poor access to diagnostic and curative services for HIV patient.

FUO is a clinical syndrome characterized of fever, for which the causes has remained unknown despite extensive diagnostic work up. The relevance of different diagnostic modalities in these patients has been an active area of research (11–16). Percutaneous liver biopsy has been shown to be useful diagnostic tool in some earlier studies (14,15). However, the indication for percutaneous liver biopsy is now less frequently encountered in HIV-infected patients, as compared to that in the 1990s. This has also contributed to the diminishing evidence-base for evaluating the utility of this procedure in the HAART era. The objective of this study was to assess the yield of percutaneous liver biopsy as a useful diagnostic modality for FUO in HIV-infected patients. Further, we sought to identify the factors associated with a greater likelihood of a positive diagnostic yield from this procedure.

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MATERIALS AND METHODS

Patients: Medical records of all HIV-infected patients who had undergone percutaneous liver biopsy from June 2003 to August 2012 at the Bamrasnaradura Infectious Diseases Institute, Thailand, were reviewed. Inclusion criteria were HIV-infected patients (i) aged ≥15 years, and (ii) presence of FUO as per the Durack and Street criteria (17) (fever ≥38.3°C for a duration of more than 4 weeks for outpatients and more than 3 days for inpatients, and confirmed HIV infection). Bedside percutaneous liver biopsy was performed using Menghini needle. Biopsy specimens were fixed in 10% formalin buffer and sent for pathological examination. Histological examination of the biopsy specimens was carried out by qualified pathologists using hematoxylin-eosin and special stains (Gomori's methenamine silver, periodic acid-Schiff, mucicarmine, and acid-fast) as appropriate. The remaining tissue was sent to a microbiology unit for bacterial, fungal, and mycobacterial culture. Ziehl-Neelsen and Wright's staining was performed for detection of acid-fast bacilli and fungi, respectively.

Demographic data, clinical data, history of HIV infection, duration of fever, treatment details, laboratory data, radiological imaging (abdominal ultrasonography

and computed tomography) reports, and results of percutaneous liver biopsy were accessed from the hospital records. Diagnoses of hepatomegaly, splenomegaly, and intraabdominal lymphadenopathy (>1 cm) was based on abdominal sonography or tomography reports. The percutaneous liver biopsy results were categorized into three groups, based on its respective diagnostic value in a particular case: (i) diagnostic (definite diagnosis from histopathological findings and staining or microbiological cultures of liver biopsy specimen), (ii) helpful (histopathological findings from liver biopsy specimens that helped in arriving at a diagnosis), and (iii) not helpful (no diagnostic contribution of liver biopsy). Diagnostic and helpful results were labeled as useful. The approval for the study was granted by the Ethics Committee for Research in Human Subjects, Department of Disease Control, Ministry of Public Health, Thailand.

Statistics: Quantitative variables are expressed as mean (±standard deviation [SD]), median (interquartile [IQR]), and in terms of frequency (percentage). All patients were categorized into out of the two groups, based on the diagnostic value of percutaneous liver biopsy: useful and not useful. In case of normally distributed continuous variables the difference between the 2 groups was analyzed with Student's *t*-test. The Mann-Whitney *U*-test was used to compare the median values of continuous variables that manifested a non-normal distribution. Categorical variables were compared by the chi-square test and Fisher's exact test, as appropriate. Logistic regression analysis was performed to identify factors associated with the likelihood of classification of percutaneous liver biopsy findings in the useful category. Variables with a *P* value (*P*) of less than 0.25 in univariate analysis were included in a multiple logistic regression model. Incidence was used to indicate percutaneous liver biopsy related complications. All statistical analyses were conducted using SPSS software, Version 15.0 (SPSS Inc. Chicago, IL, USA). A $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 101 patients who had undergone percutaneous liver biopsy, as part of the diagnostic workup for FUO, met the inclusion criteria for the study. The mean (SD) age of study subjects was 37.6 (6.9) years, of whom 60.4% were male. The median (IQR) duration of known HIV infection was 12 (2–60) months. The median (IQR) CD4 cell count was 18 (3–62) cells/mm^3. Thirty-seven out of 101 patients had a history of acquired immunodeficiency syndrome (AIDS)-defining illness. Further, 43.6% patients had received antiretroviral therapy (ART) for a median (IQR) duration of 2 (1–3) months. Non-nucleoside reverse transcriptase inhibitor-based ART was the most common treatment regimen (95.5%). The median (IQR) duration of fever prior to the procedure was 20 (8–30) days (Table 1). Percutaneous liver biopsy was categorized as diagnostic in 51 patients (50.5%), helpful in 12 (11.9%), and not helpful in 38 (37.6%). In the diagnostic group, 38 of 51 patients (74.5%) were infected with *Mycobacterium* species that included *Mycobacterium avium* (*M. avium*) complex in 18 (35.3%) patients, *Mycobacterium tuberculosis* (*M. tuberculosis*) in 8 (15.7%), and an undefined species of *Mycobacterium* in 12 (23.5%) patients. The remaining causes are shown in Table 2. Mycobacterial infections for which the species could not be defined were later diagnosed by using blood culture as being *Mycobacterium avium* complex and *Mycobacterium tuberculosis* in 3 and 2 cases, respectively. Diagnosis was obtained exclusively from percutaneous liver biopsy in 16 patients: mycobacterial infection in 11, cytomegalovirus disease in 2, malignancy in 2 (hepatocellular carcinoma and poorly differentiated carcinoma), and bacillary angiomatosis in 1.

The percutaneous liver biopsy supported the diagnosis by detecting granulomatous inflammation in 11 of 101 patients, of which 4 were later confirmed to have mycobacterial infections (one each using blood culture, lymph node culture, sputum culture, and duodenal biopsy). All patients responded well to antimycobacterial treatment. Two percutaneous liver biopsy related complications were also documented. One of the patient experienced a drop in blood pressure and a 3% decrease in hematocrit. The second patient had a 7% decline in hematocrit but had stable blood pressure. Both incidents were resolved with fluid (crystalloid or colloid) resuscitation and blood component transfusion. The site of bleeding in these patients was not documented in the patient records. After categorizing into two groups, the percutaneous liver biopsy results were considered as useful in 63 patients (62.4%), while in 38 patients (37.6%) the biopsy results were categorized as not useful. There was no significant difference ($P > 0.05$) between the two groups with respect to age, sex, HIV-transmission risk, CD4 cell count, duration of known HIV infection, percentage of patients on ART, duration of ART, ART regimens, and viral hepatitis co-infection (Table 1). On univariate analysis, duration of known HIV infection ($P = 0.116$), fever of less than 3 weeks ($P = 0.205$), elevation of serum alkaline phosphatase level (per one time elevation from the upper normal range, $P = 0.034$), total bilirubin level ($P = 0.217$), hepatomegaly ($P = 0.016$), intraabdominal lymphadenopathy ($P = 0.012$), and ART receiving ($P = 0.102$) had P of <0.25, and were included in the multivariate model (Table 3). Splenomegaly and CD4 cell count were excluded from the model because of their potential correlation with hepatomegaly and intraabdominal lymphadenopathy, respectively.

On multivariate analysis, elevation of serum alkaline phosphatase level (OR 1.27 per one time elevation from the upper normal range; 95% CI, 1.03–1.57; $P = 0.023$) and fever <3 weeks (OR, 3.82; 95% CI, 1.03–14.18; $P = 0.046$) was significantly associated with the likelihood of inclusion biopsy results in the useful category). By the time of enrollment, 12 patients had already died. Three of these patients (25.0%) fulfilled the criteria for inclusion in the useful group, while in 9 out of 12 (75.0%) patients, the biopsy findings were categorized as non-useful ($P = 0.03$).

DISCUSSION

The results from this study demonstrate the continuing relevance of percutaneous liver biopsy combined

Table 1. Baseline characteristics

Factor	All $n = 101$	Useful data $n = 63$	Not useful data $n = 38$	P value
Clinical and demographic parameter				
Sex, number (%)				
Male	61 (60.4)	38 (61.3)	23 (59.0)	0.817
Female	40 (39.6)	24 (38.7)	16 (41.0)	
Age (years), mean (±SD)	37.6 (6.9)	37.1 (6.5)	38.4 (7.6)	0.409
Transmission risk, number (%); $n = 62$				
Heterosexual	49/62 (79.0)	33/42 (78.6)	16/20 (80.0)	0.897
Homosexual	6/62 (9.7)	5/42 (11.9)	1/20 (5.0)	0.390
Intravenous drug user	7/62 (11.3)	4/42 (9.5)	3/20 (15.0)	0.456
Duration of known HIV-infection before procedure (month), median (IQR)	12 (2–60)	6 (2–42)	24 (3–60)	0.086
CD4 percentage, median (IQR)	2 (1–8)	3 (1–9)	2 (1–5)	0.251
CD4 cell count (cell/mm^3), median (IQR)	18 (3–62)	20 (3–75)	15 (4–28)	0.297
Duration of fever before procedure (day), median (IQR)	20 (8–30)	15 (8–30)	22 (9–31)	0.196
Hepatitis B virus co-infection, number (%); $n = 55$	8/55 (14.5)	5/36 (13.9)	3/19 (15.8)	0.849
Hepatitis C virus co-infection, number (%); $n = 47$	8/47 (17.0)	5/33 (15.2)	3/14 (21.4)	0.601
Received ART before procedure, number (%)	44 (43.6)	31 (49.2)	13 (34.2)	0.100
Nevirapine based	31 (30.7)	22 (34.9)	9 (23.7)	0.188
Efavirenz based	11 (10.9)	7 (11.1)	4 (10.5)	0.871
Protease inhibitors based	2 (2.0)	2 (3.2)	0	0.257
Period of ART initiation before procedure (month), median (IQR)	2.0 (1.0–3.0)	2.0 (1–3.5)	1.0 (0.5–3.0)	0.197
Laboratory parameter				
White blood cell from complete blood count ($\times 10^3$/mm^3), median (IQR)	5.2 (3.0–7.6)	5.3 (3.4–7.5)	5.0 (2.7–8.0)	0.727
Hemoglobin (g/dL), median (IQR)	9.2 (8.0–10.3)	9.3 (7.4–10.3)	9.0 (8.3–10.5)	0.383
Platelet count ($\times 10^3$/mm^3), median (IQR)	269 (154–370)	274 (152–380)	244 (156–347)	0.823
Aspartate aminotransferase level (U/L), median (IQR)	72 (45–116)	82 (44–119)	62 (45–115)	0.529
Alanine aminotransferase level (U/L), median (IQR)	46 (28–68)	45 (26–64)	47 (28–97)	0.360
Alkaline phosphatase level (U/L), median (IQR)	529 (315–989)	627 (374–1032)	397 (267–714)	0.030
Total bilirubin level (mg/dL), median (IQR)	1.0 (0.5–2.5)	0.9 (0.5–2.3)	1.0 (0.6–2.8)	0.242
Direct bilirubin level (mg/dL), median (IQR)	0.6 (0.2–1.6)	0.5 (0.2–1.4)	0.6 (0.2–2.4)	0.410
Albumin level (g/dL), median (IQR)	2.8 (2.4–3.1)	2.8 (2.4–3.1)	2.9 (2.4–3.2)	0.810
Radiological finding parameter; $n = 83$				
Hepatomegaly, number (%)	69/83 (83.1)	49/54 (90.7)	20/29 (69.0)	0.012
Splenomegaly, number (%)	42/83 (50.6)	31/54 (57.4)	11/29 (31.9)	0.091
Intraabdominal lymphadenopathy, number (%)	30/83 (36.3)	25/54 (46.3)	5/29 (17.2)	0.009

Table 2. Definite causes of FUO between naïve and ART-receiving patients obtained from percutaneous liver biopsy

Cause	All $n = 51$ (%)	Naïve $n = 27$ (%)	ART-receiving $n = 24$ (%)	P value
				0.227
M. avium complex infection	18 (35.3)	7 (25.9)	11 (45.8)	
Mycobacterial infection (species could not be defined)	12 (23.5)	7 (25.9)	5 (20.8)	
Tuberculosis	8 (15.7)	5 (18.5)	3 (12.5)	
Cryptococcosis	5 (9.8)	1 (3.7)	4 (16.7)	
Histoplasmosis	3 (5.9)	3 (11.1)	0	
Cytomegalovirus disease	2 (3.9)	1 (3.7)	1 (4.2)	
Malignancy	2 (3.9)	2 (7.4)	0	
Bacillary angiomatosis	1 (2.0)	1 (3.7)	0	

Table 3. Univariate and multivariate analyses of factors associated with attainment of useful data from percutaneous liver biopsy

Factor	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Duration of known HIV infection before procedure	0.99 (0.98–1.00)	0.116	0.99 (0.98–1.01)	0.378
Fever < 3 weeks	1.70 (0.75–3.87)	0.205	3.82 (1.03–14.18)	0.046
Received ART before procedure	2.00 (0.87–4.59)	0.102	1.98 (0.59–6.59)	0.268
Alkaline phosphatase level, per one time elevated from upper normal range	1.14 (1.01–1.28)	0.034	1.27 (1.03–1.57)	0.023
Total bilirubin level	0.94 (0.84–1.04)	0.217	0.85 (0.72–1.00)	0.052
Hepatomegaly	4.41 (1.31–14.80)	0.016	2.28 (0.50–10.51)	0.290
Intraabdominal lymphadenopathy	4.14 (1.38–12.46)	0.012	2.57 (0.74–9.02)	0.136

with microbiological studies for establishing the causation of FUO in HIV-infected patients. On multivariate analysis, elevation of serum alkaline phosphatase level and fever <3 weeks was significantly associated with increased likelihood of diagnostic yield from percutaneous liver biopsy specimens. Mycobacterial infection was the most common cause of FUO in this study. Further, *M. avium* complex appeared to have a higher prevalence than *M. tuberculosis*. We assumed that percutaneous liver biopsy-related bleeding complications occurred in 2% of patients. However, this assumption could not be confirmed as no bleeding sites were documented in the patient records.

In this study we sought to assess the clinical utility of percutaneous liver biopsy in diagnosing the cause of FUO in HIV-infected patients in the era of HAART. The diagnostic yield of percutaneous liver biopsy in our study was comparable to that reported by earlier studies conducted in the pre-HAART era (14,15,18), but was higher than that reported from France (19). In addition, the diagnostic yield obtained in this series was much higher than that reported in non-HIV patients (20). As compared to bone marrow studies, which have a reported diagnostic yield of 5–38% for FUO in HIV-infected patients (12,13,21–23), the corresponding diagnostic yield of percutaneous liver biopsy in our study was 62%.

Despite the increasing trend in coverage of HAART therapy in HIV patients, access to ART services continues to be challenge in resource-limited countries. In such settings, the incidence of FUO and opportunistic infections among HIV-infected patients is likely to remain high. Our findings support the continuing relevance of percutaneous liver biopsy as a useful tool for establishing the causes of FUO in these patients, even in the HAART era. Our finding are consistent with those of previous studies (14,15,18) that have also demonstrated the particular value of this procedure in patients with elevated serum alkaline phosphatase. Since elevated serum alkaline phosphatase is indicative of hepatic infiltrative pathology (24,25), percutaneous liver biopsy in patients with FUO is more likely to lead to a specific diagnosis. In contrast to the results reported by Garcia-Ordonez, et al. (15), we found no correlation of hepatosplenomegaly or intraabdominal lymphadenopathy with a higher likelihood of diagnostic yield of percutaneous liver biopsy. This might be explained by two possible reasons. First, most of our patients had advanced HIV infection, with likely attenuation of secondary lymphoid organs owing to fibrosis spreading throughout the T-cell zone, thus resulting in the smaller size of secondary lymphoid organs (26). Second, subjective differences in the interpretation of the results could also have contributed to the differences in findings. The association of fever <3 weeks with the likelihood of utility of liver biopsy could be explained by the relatively active immune response of the hepatic issue in the early stages of disseminated infection, which prevents the development of chronic infection in the liver (27). Therefore, the infection load in the liver is likely reduce with increasing duration of fever. It follows that any delay in resorting to percutaneous liver biopsy after failure of non-invasive investigations may decrease the likelihood of a positive yield from biopsy specimens. Interestingly, despite no observable sign of disseminated infection, mycobacterial infection was isolated exclusively from percutaneous liver biopsy specimen in 11 patients. In these patients, the infection could only be detected by culture or AFB staining of the liver tissue. These patients had normal chest radiography findings, no peripheral lymphadenopathy, and negative blood cultures for mycobacteria. The route of hepatic mycobacterial infection might be caused by a less common type: i.e., local infection with dissemination via the portal vein as against the hepatic artery, as seen in the miliary form of mycobacterial infection (28,29). Although Heller et al. (30,31) demonstrated the value of abdominal ultrasonography, a noninvasive technique, for identifying extrapulmonary tuberculosis in HIV-infected patients, (especially in abdominal tuberculosis), it does not provide for microbiological or histological confirmation. Thus, non-tubercular mycobacteria, endemic fungi, and lymphoma that can mimic extrapulmonary tuberculosis are liable to be missed. The opportunity to establish a definitive diagnosis with microbiological and histopathological examination, including molecular study of liver biopsy specimens is the foremost advantage of this method. However, the invasive nature of the investigations a shortcoming. With the advancement of various diagnostic technologies, percutaneous liver biopsy may not be the first diagnostic modality of choice for FUO associated with HIV infection. Nevertheless, it is likely to be helpful in case of failure of other non-invasive diagnostic tools.

Our study suggests the continuing occurrence of AIDS-defining opportunistic infections as a major cause of FUO despite the wider availability of HAART. The reasons for persistence of these infections could be the insufficient ART coverage and initiation of ART at a very low CD4 cell count, which renders patients vulnerable to opportunistic infections in the early months after ART initiation. This scenario is likely to prevail in low-income and some middle-income countries. Among the group of patients from whom useful data could not be obtained by percutaneous liver biopsy, 14 patients had received ART prior to the procedure. No final diagnosis was made in 7 patients (spontaneously recovery in 2, death in 2, and loss to follow up in 3). Some of these patients might have experienced immune reconstitution inflammatory syndrome (IRIS). We were not able to assess the incidence of IRIS due to lack of HIV RNA testing and results in the hospital records.

This study has some limitations. The retrospective nature of the study is a major limitation that could have contributed to a selection bias. The abnormal liver function tests may have led physicians to consider percutaneous liver biopsy, thus increasing the possibility of a definite diagnosis from liver biopsy specimen. Nevertheless, the study did demonstrate the potential of percutaneous liver biopsy as a useful diagnostic modality in HIV-infected patients with FUO and high alkaline phosphatase levels. Secondly, the study did not employ molecular diagnostics owing the relative lack of its availability at the time of performing percutaneous liver biopsy. Lastly, we could not exclude the possibility IRIS, which is a potential cause of FUO in HIV-infected patients with recent ART initiation. In settings with a high ART coverage or low incidence of mycobacterial

infection, the diagnostic yield of percutaneous liver biopsy may not be comparable to that obtained in our study.

In conclusion, the possibility of advanced diagnostic technology gradually replacing the more invasive diagnostic methods cannot be denied. However, microbiological examination of percutaneous liver biopsy specimen is likely to be useful in establishing a definitive diagnosis in case of FUO in HIV-infected patients, particularly those with elevated serum alkaline phosphatase level and/or fever <3 weeks, at least in areas where mycobacterial infection is a distinct possibility. Careful monitoring after performing the procedure is advised owing to the possibility of complications. AIDS-defining opportunistic infections continue to be an important cause of FUO in the HAART era, especially in countries where early identification of HIV-infected patients continues to be significant challenge. Thus, in addition to increasing ART access, early detection of HIV infection should be considered as an important issue.

Conflict of interest None to declare.

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