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Hepatic Tuberculosis : A Clinico-Pathological Study

Ratha-korn Vilaichone, M.D., Ph.D.*
Varocha Mahachai, M.D., F.R.C.P.(C), F.A.C.G.**

ABSTRACT

Objective: Hepatic tuberculosis remains the world wide problem especially in the AIDS era. The aim of this study was to compare the clinico-pathological manifestations of hepatic tuberculosis in immunocompromised and immunocompetent patients.

Patients and Methods: We reviewed retrospectively 20 Thai patients with hepatic tuberculosis during the year 1993-2000. There were 12 immunocompromised patients (10 HIV males, 1 SLE male, 1 SLE female) and 8 immunocompetent patients (6 males, 2 females). The diagnosis of Mycobacterium tuberculosis (M. tb) were the combination of demonstrate the organism in hemo- or specimen culture, histopathology (positive acid fast bacilli) and rapid identification of M.tb from nested polymerase chain reaction (nPCR) assay based on amplification of the IS 6110 insertion sequences.

Results: The clinical features were similar in both groups with fever, weight loss and hepatomegaly as the main manifestations. The biochemical findings were also similar but the alkaline phosphatase (ALP) was significantly higher in the immunocompromised group ($p < 0.001$). Non-caseating granuloma without detection of acid fast bacilli was a common finding in both groups. The nested PCR assay increased the sensitivity from 49 percent to 86 percent compare to the regular PCR assay but specificity was 100 percent in both techniques. The mortality was significantly higher in immunocompetent patients ($p < 0.05$) due to the extreme age and severe coexisting diseases.

Conclusion: Fever, weight loss, hepatomegaly, disproportionate elevation of ALP and reverse A/G ratio were common in hepatic tuberculosis. A disproportionate elevation of ALP was significantly higher in immunocompromised hosts. Nested-PCR assay showed good sensitivity and specificity in the diagnosis of this disease.

Key words : Hepatic tuberculosis, clinico-pathological study

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** Gastroenterology Unit, Department of Medicine, Thammasat University Hospital, Pathumthani*
*** Gastroenterology Unit, Department of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand*

INTRODUCTION

Hepatic tuberculosis is not uncommon and has a worldwide distribution[1]. It is diagnosed clinically in 50-80 percent of all patients dying of pulmonary tuberculosis and in up to 91 percent at autopsy[2,3]. Hepatic tuberculosis can be classified into miliary and localized forms[2,4,5]. The former is associated with miliary dissemination which occurs from hematogenous spreading via the hepatic artery. In the local form, bacteria reach the liver from the intestine via the portal vein. Both forms of hepatic tuberculosis have been seen in normal and immunocompromised hosts. The aim of this study was to compare the clinico-pathological manifestations of hepatic tuberculosis in immunocompromised and immunocompetent patients.

PATIENTS AND METHODS

From January 1993 to October 2000, twenty patients with proven hepatic tuberculosis were diagnosed in Chulalongkorn university hospital. They included 12 immunocompromised and 8 immunocompetent patients. The clinical manifestations, biochemical tests, radiological features and pathological findings were compared. The diagnosis of Mycobacterium tuber culosis (M. tb) were the combination of demonstrate the organism in hemo- or specimen culture, histopathology (positive acid fast bacilli) and rapid identification of M.tb from nested polymerase chain reaction (nPCR) assay based on amplification of the IS 6110 insertion sequences[6]. Serum albumin, globulin, serum aspartate aminotransferase (AST), serum alanine aminotranferase (ALT), alkaline phosphatase (ALP) and bilirubin were determined using routine automated techniques. Liver histopathology findings were re-examined in all case. All tissue sections were stained with Ziehl- Neelsen stain for acid fast bacilli and were sent for M. tb DNA extraction for the PCR assay. Hemoculture and liver tissue culture for M. tb were carried out in all cases.

Statistical analysis was performed by the paired t test, chi-square test or or Fisher's exact test depending on the data set of concern. A p value of less than 0.05 was accepted as statistically significant.

RESULTS

All twenty patients with hepatic tuberculosis satisfied the diagnostic criteria. They included 12 immunocompromised patients including 10 HIV males, 1 SLE male and 1 SLE female (mean age of 35.3 years, range 13 to 50 years) and all of HIV patients had CD4+ lymphocyte count less than 200 (mean 98, range 45 to 191). There are 8 immunocompetent patients including 6 males and 2 females (mean age of 36.4 years, range 0.5 to 72 years). All of the SLE patients are receiving high dose prednisolone (1 mg/kg/day). The immunocompromised group had pulmonary tuberculosis (TB) in 5 patients (42%), TB involved lymph nodes in 4 patients (33%) and TB involve bone marrow in 2 patients (17%). For immunocompetent group, they had pulmonary TB in 3 patients (38%). The clinical features of both groups are compared in Table 1. The symptoms and signs were similar with fever, hepatomegaly, abdominal pain and loss of body weight as the main manifestations. Biochemical findings of the immunocompromised and immunocompetent patients are compared in Table 2. The characteristic features in both groups were reverse albumin and globulin (A/G) ratios (0.8 ± 0.4 vs. 0.7 ± 0.09; $p > 0.05$) and elevated bilirubin values (1.8 ± 3.8 vs. 2.5 ± 3.1 mg/dL; $p > 0.05$).

Immunocompromised patients had lower levels

Table 1 Presenting symptoms and signs in hepatic tuberculosis

	Immunocompromised (12)	Immunocompetent (8)	p-value
Fever	12 (100%)	8 (100%)	NS
Hepatomegaly	10 (83.3%)	6 (75%)	NS
Abdominal pain	9 (75%)	3 (37.5%)	NS
Weight loss	7 (58.3%)	5 (62.5%)	NS
Spleenomegaly	5 (41.7%)	3 (37.5%)	NS
Jaundice	4 (33.3%)	0	NS
Diarrhea	1 (8.3%)	1 (12.5%)	NS

Table 2 Biochemical tests in hepatic tuberculosis

	Immunocompromised (12)	Immunocompetent (8)	p-value
ALP (U/L)	1,374.6 ± 714.4	472.2 ± 209.6	<0.001*
AST (U/L)	99.1 ± 48.7	263.7 ± 334.4	0.12
ALT (U/L)	55.5 ± 26	224.4 ± 308.3	0.09
Albumin (g/dL)	3.0 ± 0.5	3.2 ± 0.47	0.13
Globulin (g/dL)	3.9 ± 0.9	4.1 ± 0.6	0.64
A/G	0.8 ± 0.4	0.7 ± 0.09	0.26
Bilirubin (mg/dL)	1.8 ± 3.8	2.5 ± 3.1	0.32

[#]*Mean ± SD*

Table 3 Ultrasonographic findings in hepatic tuberculosis

	Immunocompromised (11)	Immunocompetent (7)	p-value
Diffuse increase echogenicity	7 (63.6%)	3 (42.8%)	NS
Multiple hypoechoic lesions	2 (18.1%)	1 (14.3%)	NS
Calcifications	0	2 (28.5%)	NS
Hepatomegaly	2 (18.1%)	2 (28.5%)	NS
Ascitis	2 (18.1%)	4 (57.1%)	NS

Table 4 Histopathological findings in hepatic tuberculosis

	Immunocompromised (12)	Immunocompetent (8)	p-value
Non-caseous granuloma	7 (58.3%)	4 (50%)	NS
Caseous grauloma	5 (41.6%)	4 (50%)	NS
AFB +ve	4 (33.3%)	2 (25%)	NS
Fatty change	0	1 (12.5%)	NS

of ALT (55.5 ± 26 vs 224.8 ± 308.3 U/L; p >0.05), AST (99.1 ± 48.7 vs. 263.7 ± 334.4; p >0.05) but significantly higher levels of serum ALP (1,374.6 ± 714.4 vs. 472.2 ± 209.6; p <0.001) than immunocompetent patients. The ultrasonographic features of both groups are shown in Table 3 and there were no significant differences. Table 4 shows histopathological findings. There were no significant differences with respect to granulomata, caseation (Figure 1), number of acid fast bacilli (Figure 2) and fatty changes. Ziehl-Neelsen stains of liver tissue for acid fast bacilli was done in all cases but was positive in only six (30%).

There were 14 patients who underwent liver tissue DNA extraction with rapid identification of M. tb by PCR and nPCR assay (Figure 3) based on amplification of the IS 6110 insertion sequences. The nested

Figure 1 Caseous granuloma

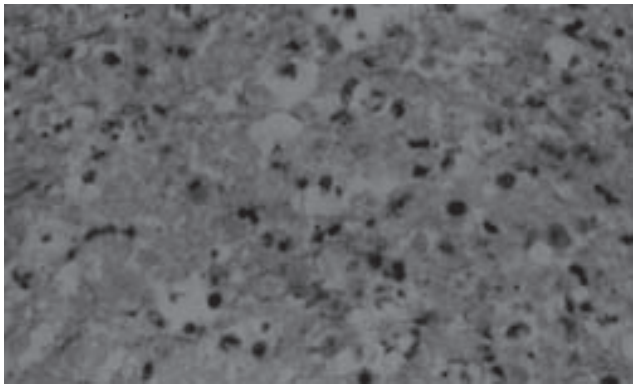

Figure 2 Multiple acid fast bacilli

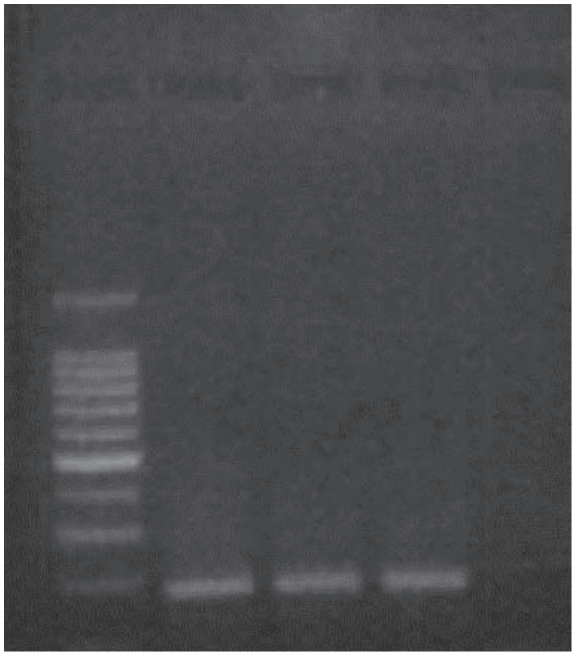

Figure 3 Nested PCR assay
A DNA marker; B positive control
C and D Liver specimens; E negative control

PCR assay had better sensitivity than the regular PCR assay (86 vs 49%) but showed the same specificity of 100 percent. The mortality was significantly higher in the immunocompetent group (38 vs 25%; p <0.05) as summarized in Table 5.

DISCUSSION

These results demonstrated a wide range of non-specific clinical manifestations in patients with hepatic tuberculosis. There were no consistently present symptoms or signs, and radiologic features[2,7-10]. However, our results show that the common biochemical features of hepatic tuberculosis was a reversed A/G ratio and elevation of serum ALP as previous observations[7,11,12]. Furthermore, significantly higher of disproportionate elevation of serum ALP was first observe in immunocompromised host. These findings were useful in suspecting hepatic tuberculosis.

The spectrum of ultrasound findings ranged from hepatomegaly diffusely increased parenchymal echogenicity to multiple hypoechoic lesions in the liver. Although calcification was a suggestive finding in tuberculosis, we noted it in only 22.2 percent of subjects. Computed tomography (CT) and magnetic resonance (MRI) imaging demonstrated liver lesions and involvement of other organs such as the bowel, peritonium and lymph nodes[13,14].

Noncaseating granulomata without detectable acid fast bacilli were a common pathological feature in both groups (55%). Caseous granuloma with positive acid fast staining was found, in only 30 percent of patients. However, caseous granulomata can also occur with atypical mycobacterial infections[15]. Our immunocompromised patients had multiple organ involvement such as of lungs, bone marrow and lymph

Table 5 Causes of death in hepatic tuberculosis

	Immunocompromised (3)	Immunocompetent (3)#	
GI bleeding	-	2	
ARDS*	-	1	
Acute renal failure	-	1	
Disseminated TB	3	-	
Mortality rate	25%	38%	p-value <0.05

#*one patient had both GI bleeding and ARDS.*
**ARDS = Acute respiratory distress syndrome*

nodes more commonly than immunocompetent subjects. However, the difference was not statistically significant. Patients with SLE have a 25-50 percent lifetime risk of developing abnormal liver function tests and the most common cause is drug induced hepatitis[16]. Granuloma formation can be occasionally seen as an active manifestation of SLE and severe fatal liver disease does occur[17,18]. Furthermore, a granulomatous liver disease may represent active manifestation of SLE[17]. It's quite difficult to differential these granulomatous lesions from tuberculosis unless the patients had found the finding positive M. tb hemoculture or liver specimen cultures or on rapid identification of M.tb from PCR assay.

The nPCR assay showed high sensitivity (86%) and specificity (100%) in the diagnosis of hepatic tuberculosis in our study. PCR is a valuable tool for the demonstration of mycobacterial DNA in tissues[19] which may be more reliable than histopathology for detecting M. tb in a liver biopsy[20]. Hence, liver biopsy combined with histopathology, culture and nPCR are appropriate when hepatic tuberculosis is suspected. The mortality was significantly higher in our immunocompetent patients. This can be explained by their extreme age and severe coexisting diseases as summarize in Table 5. Treatment of hepatic tuberculosis is similar to that used for pulmonary tuberculosis. Quadruple therapy (using four anti-tuberculosis drugs) is recommended, generally for 1 year[21]. For patients with obstructive jaundice, in addition to anti-tuberculous treatment, biliary decompression should be performed either by stent insertion during endoscopic retrograde cholangiopancreatology, by percutaneous transhepatic biliary drainage or by surgical decompression whenever feasible.

In summary, Fever, weight loss, hepatomegaly, disproportionate elevation of ALP and reverse A/G ratio might be suggeted hepatic tuberculosis. A disproportionately elevated ALP is common in immunocompromised hosts. nPCR assays show good sensitivity and specificity in the diagnosis of this disease.

REFERENCES

1. McCluggage WG, Sloan JM. Hepatic granuloma in Northern Ireland: a thirteen year review. Histopathology 1994; 25: 219-28.
2. Chien RN, Lin PY, Liaw YF. Hepatic tuberculosis: comparison of miliary and local form. Infection 1995; 1: 5-8.
3. Gelb AF, Leffler C, Brewin A, *et al*. Miliary tuberculosis. Am Rev Resp Dis 1973; 108: 1327-32.
4. Herman P, Pugliese V, Laurino Neto R, *et al*. Nodular form of local hepatic tuberculosis: case report. J Trop Med Hyg 1995; 98: 141-2.
5. Oliva A, Duarte B, Jonasson O, *et al*. The nodular form of local hepatic tuberculosis. A review. J Clin Gastroenterol 1990; 12: 166-73.
6. du Plessis DG, Warren R, Richardson M, *et al*. Demonstration of reinfection and reactivation in HIV-negative autopsied cases of secondary tuberculosis: multilesional genotyping of Mycobacterium tuberculosis utilizing IS 6110 and other repetitive element-based DNA fingerprinting. Tuberculosis (Edinb) 2001; 81: 211-20.
7. Hersch C. Tuberculosis of the liver. A study of 200 cases. S Afr Med J 1964; 38: 857-63.
8. Alvarez SZ, Carpio R. Hepatobiliary tuberculosis. Dig Dis Sci 1983; 28: 193-200.
9. Amaris J, Kardache M, Soyer P, *et al*. Radiological aspects of hepatic tuberculoma 3 cases. Gastroenterol Clin Biol 1997; 21: 888-92.
10. Jain R, Sawhney S, Gupta RG, *et al*. Sonographic appearances and percutaneous management of primary tuberculous liver abscess. J Clin Ultrasound 1999; 27: 159-63.
11. Essop AR, Posen JA, Hodkinson JH, *et al*. Tuberculosis hepatitis: a clinical review of 96 cases. Q J Med 1984; 53: 465-77.
12. Sabharwal BD, Malhotra N, Garg R, *et al*. Granulomatous hepatitis : a retrospectiv study. Indian J Pathol Microbiol 1995; 38: 413-6.
13. Gulati MS, Sarma D, Paul SB. CT appearences in abdominal tuberculosis. A pictorial essay. Clin Imaging 1999; 23: 51-9.
14. Fan ZM, Zeng QY, Huo JW, *et al*. Macronododular multiorgans tuberculoma: CT and MR appearances. J Gastroenterol 1998; 33: 285-8.
15. Orestein MS, Tavitian A, Yonk B. Granulomatous involvement of the liver in patients with AIDS. Gut 1985; 26: 1220-25.
16. an Hoek B. The spectrum of liver disease in systemic lupus erythematosus. Neth J Med 1996; 48: 244-53.
17. Feurle GE, Broker HJ, Tschhargane C. Granulomatous hepatitis in systemic lupus erythematosus: report of a case. Endoscopy 1982; 14: 153-4.
18. Runyon BA, LaBrecque DR, Anuras S. The spectrum of liver disease in systemic lupus erythematosus. Report of 33 histologically-proved cases and review of the literature. Am J Med 1980; 69: 187-94.
19. Diaz ML, Herrera T, Lopez-Vidal Y, *et al*. Polymerase chain reaction for the detection of Mycobacterium tuberculosis DNA in tissue and assessment of its utility in the diagnosis of hepatic granulomas. J Lab Clin Med 1996; 127: 359-63.
20. Akcan Y, Tuncer S, Hayran M, *et al*. PCR on disseminated tuberculosis in bone marrow and liver biopsy specimens: correlation to histopathological and clinical diagnosis. Scand J Infect Dis 1997; 29: 271-4.
21. Alvarez SZ. Hepatobiliary tuberculosis. J Gastroenterol Hepatol 1998; 13: 833-9.