# Clinical Spectrum of Hepatic Tuberculosis : Comparison between Immunocompetent and Immunocompromised Hosts

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**Abstract**

**Background :** Hepatic tuberculosis has been reported in normal and immunocompromised hosts. However, have found no published comparisons between these two groups of subjects with hepatic tuberculosis have been found. The aim of this study was to compare the clinical manifestations, biochemical tests, radiologic features and pathological findings of hepatic tuberculosis in immunocompromised and immunocompetent patients.

**Method :** The authors reviewed retrospectively 20 patients with hepatic tuberculosis admitted between January 1993 and October 2000 to Chulalongkorn University Hospital, Thailand. There were 12 immunocompromised patients (10 HIV-infected males, 1 systemic lupus erythematosus (SLE) male, 1 SLE female) and 8 immunocompetent patients (6 males, 2 females). The clinical manifestations, biochemical tests, radiologic features and pathological findings were compared between these 2 groups. The diagnosis of *Mycobacterium tuberculosis (M. tb)* was the combination of a demonstrated 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 ($p < 0.001$). Hepatomegaly and diffuse increased echogenicity were common in both groups. Ascitis and calcifications were found more commonly in the immunocompetent subjects, although the differences were not statistically significant. 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 per cent to 86 per cent compared to the regular PCR assay but specificity was 100 per cent 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 the immunocompromised hosts. Nested PCR assay showed good sensitivity and specificity in the diagnosis of this disease.

**Key word :** Hepatic Tuberculosis, Immunocompetent, Immunocompromised

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Tuberculosis is one of the most common and well-described infectious diseases, with a vast spectrum of clinical manifestations. Involvement of the liver, hepatic tuberculosis, is not uncommon and has a worldwide distribution[1]. It is diagnosed clinically in 50-80 per cent of all patients dying of pulmonary tuberculosis and in up to 91 per cent at autopsy[2,3]. Hepatic tuberculosis can be classified into miliary and localized forms[2,4,5]. The former is associated with miliary dissemination. Hematogenous dissemination occurs *via* the hepatic artery. Bacteria reach the liver from the intestine *via* the portal vein in the local form. Both forms of hepatic tuberculosis have been seen in normal and immunocompromised hosts. To the authors' knowledge, this is the first study that investigated immunocompromised and immunocompetent subjects with hepatic tuberculosis.

## PATIENTS AND METHOD

From January 1993 to October 2000, twenty patients with proven hepatic tuberculosis were diagnosed in King Chulalongkorn Memorial 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 tuberculosis (M. tb)* was the combination of a demonstrated 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 every case. All tissue sections were stained with Ziehl- Neelsen stain for acid fast bacilli and sent for *M. tb* DNA extraction by PCR assay. Hemoculture and liver tissue culture for *M. tb* were carried out in all cases.

Statistical analysis was carried out using Student's test or Fisher's exact test where appropriate.

## RESULTS

All twenty patients with hepatic tuberculosis satisfied the diagnostic criteria. They included 12 immunocompromised patients including 10 HIV-infected males, 1 SLE male and 1 SLE female (mean age of 35.3 years, range 13 to 50 years) and all the HIV patients had CD4+ lymphocyte count less than 200

(mean 98, range 45 to 191). There were 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 a high dose of 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 involved bone marrow in 2 patients (17%). The immunocompetent group 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 reversed 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 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 (1374.6 ± 714.4 *vs* 472.2 ± 209.6; $p < 0.001$) than the immunocompetent patients. The ultrasonographic features of both groups are shown in Table 3 and there were no significant differences. Table 4 shows the histopathological findings. There were no significant differences with respect to granulomata, caseation (Fig. 1), number of acid-fast bacilli (Fig. 2) and fatty changes.

**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 | 0 | NS |
| Diarrhea | 1 | 8.3 | 1 | 12.5 | NS |

**Table 2. Biochemical tests in hepatic tuberculosis.**

| | Immunocompromised(12) (Mean ± SD) | Immunocompetent(8) (Mean ± SD) | P-value |
|---|---|---|---|
| ALP (U/L) | 1374.6 ± 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 |

**Table 3. Ultrasonographic findings in hepatic tuberculosis.**

| | Immunocompromised(11) | % | Immunocompetent(7) | % | P-value |
|---|---|---|---|---|---|
| Diffuse increased echogenicity | 7 | 63.6 | 3 | 42.8 | NS |
| Multiple hypoechoic lesions | 2 | 18.1 | 1 | 14.3 | NS |
| Calcifications | 0 | 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 | 0 | 1 | 12.5 | NS |

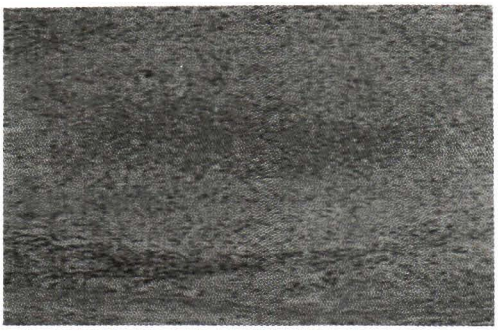

**Fig. 1. Caseous granuloma.**

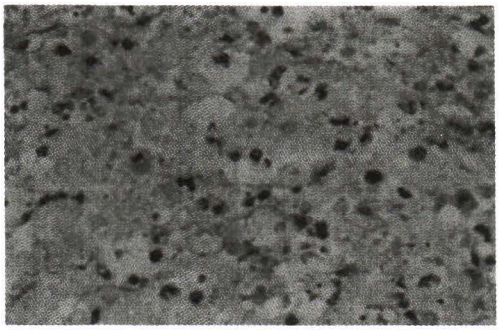

**Fig. 2. Multiple acid-fast bacilli.**

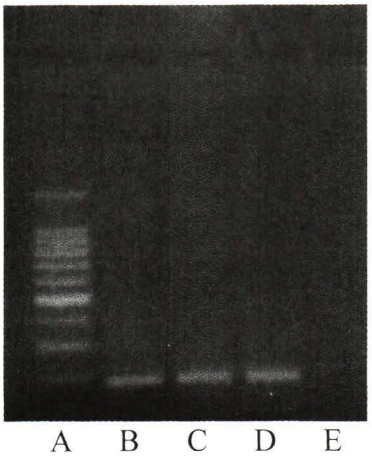


**Fig. 3. Nested PCR assay.**

**A = DNA marker, B = positive control,**
**C and D = Liver specimens, E = negative control**

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 (Fig. 3) based on amplification of the IS 6110 insertion sequences. The nested PCR assay had better sensitivity than the regular PCR assay (86 *vs* 49%) but showed the same specificity of 100 per cent. 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, the present results show that the common biochemical features of hepatic tuberculosis was a reversed A/G ratio and elevation of serum ALP as previously observed(7,11,12). Furthermore, a signi-

**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

ficantly higher disproportionate elevation of serum ALP was first observed 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, the authors noted it in only 22.2 per cent of the 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 per cent of patients. However, caseous granulomata can also occur with atypical mycobacterial infections(15). The immunocompromised patients in the present study had multiple organ involvement such as lungs, bone marrow and lymph nodes more commonly than the immunocompetent subjects. However, the difference was not statistically significant. Patients with SLE have a 25-50 per cent life-time 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, granulomatous liver disease may represent active manifestation of SLE(17). It's quite difficult to differentiate these granulomatous lesions from tuberculosis unless the patients had the finding of positive *M. tb* hemoculture or liver specimen cultures or rapid identification of *M. tb* from PCR assay.

The nPCR assay showed a high sensitivity (86%) and specificity (100%) in the diagnosis of hepatic tuberculosis in the present 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 the immunocompetent patients in the present study. This can be explained by their extreme age and severe coexisting diseases as summarized in Table 5. Treatment of hepatic tuberculosis is similar to that 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 sugget hepatic tuberculosis. A disproportionately elevated ALP is common in immunocompromised hosts. nPCR assays show good sensitivity and specificity in the diagnosis of this disease.

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# ลักษณะทางคลินิกของวัณโรคตับเปรียบเทียบระหว่างผู้ป่วยที่มีภูมิคุ้มกันปกติและผู้ป่วยที่มีภูมิคุ้มกันเสื่อม

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การศึกษานี้มีวัตถุประสงค์เพื่อศึกษา ลักษณะทางคลินิกของวัณโรคตับเปรียบเทียบระหว่างผู้ป่วยที่มีภูมคุ้มกันปกติและผู้ป่วยที่มีภูมิคุ้มกันเสื่อมโดยศึกษาผู้ป่วยจำนวน 20 คน ที่มารับการรักษาที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนมกราคม พ.ศ. 2536 ถึง เดือนตุลาคม พ.ศ. 2543 แบ่งเป็นผู้ป่วยที่มีภูมิคุ้มกันเสื่อม 12 คน (ผู้ป่วยเอดส์ 10 คน, ผู้ป่วยลูปัส 2 คน) และผู้ป่วยที่มีภูมิคุ้มกันปกติ 8 คน โดยผู้ป่วยทุกคนจะได้รับการบันทึกอาการทางคลินิก ผลตรวจทางห้องปฏิบัติการ ผลตรวจทางรังสีวิทยาและผลตรวจทางพยาธิวิทยา การวินิจฉัยวัณโรคตับอาศัยผลการเพาะเชื้อจากเลือดหรือชิ้นเนื้อตับพบเชื้อวัณโรค หรือการตรวจชิ้นเนื้อตับด้วยปฏิกิริยาลูกโซ่โพลีเมอเรสให้ผลบวก จากผลการศึกษาพบว่าอาการทางคลินิกของผู้ป่วยทั้ง 2 กลุ่ม คล้ายกันซึ่งประกอบไปด้วย ไข้ น้ำหนักลดและตับโต ผลตรวจการทำงานของตับพบว่าคล้ายคลึงกันยกเว้นระดับของ alkaline phosphatase ที่สูงผิดปกติเมื่อเทียบกับค่า bilirubin พบในผู้ป่วยที่มีภูมิคุ้มกันเสื่อม สูงกว่าผู้ป่วยที่มีภูมิคุ้มกันปกติอย่างมีนัยสำคัญทางสถิติ ผลตรวจทางรังสีวิทยา และผลตรวจทางพยาธิวิทยาพบว่าไม่มีความแตกต่างกันระหว่างผู้ป่วยทั้ง 2 กลุ่ม การตรวจพบเชื้อวัณโรคในชิ้นเนื้อตับโดย ปฏิกิริยาลูกโซ่โพลีเมอเรสแบบ nested มีความไวสูงกว่าการตรวจแบบปกติ (ร้อยละ 49 เทียบกับร้อยละ 86 ตามลำดับ) อย่างไรก็ดีความจำเพาะของ 2 วิธีนี้ไม่มีความแตกต่างกัน (ร้อยละ 100) อัตราตายของผู้ป่วยที่มีภูมิคุ้มกันปกติสูงกว่าผู้ป่วยที่มีภูมิคุ้มกันเสื่อมอย่างมีนัยสำคัญทางสถิติ ซึ่งอธิบายจากผู้ป่วยที่มีภูมิคุ้มกันปกติมีอายุที่สูงกว่า นอกจากนี้ยังมีภาวะแทรกซ้อนที่รุนแรงร่วมด้วย โดยสรุปการศึกษานี้พบว่า ไข้ น้ำหนักลดและตับโต เป็นอาการที่พบได้บ่อยในผู้ป่วยวัณโรคตับ นอกจากนี้พบว่าระดับของ alkaline phosphatase ที่สูงผิดปกติเมื่อเทียบกับค่า bilirubin พบในผู้ป่วยที่มีภูมิคุ้มกันเสื่อมนั้นสูงกว่าผู้ป่วยที่มีภูมิคุ้มกันปกติอย่างมีนัยสำคัญทางสถิติ และการตรวจพบเชื้อวัณโรคในชิ้นเนื้อตับโดย ปฏิกิริยาลูกโซ่โพลีเมอเรสแบบ nested นั้น มีความไวสูงกว่าการตรวจแบบปกติ

**คำสำคัญ** : วัณโรคตับ, ผู้ป่วยภูมิคุ้มกันปกติ, ผู้ป่วยภูมิคุ้มกันเสื่อม

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