Liver Biopsy in a Tuberculosis Hospital

WILLIAM B. BUCKINGHAM, M.D., GEORGE C. TURNER, M.D., F.C.C.P.,
WILLIAM B. KNAPP, M.D., QUENTIN D. YOUNG, M.D., F.C.C.P.
and FENTON SCHAFFNER, M.D.

Oak Forest, Illinois

Histologic examination of liver tissue obtained by needle biopsy has vastly improved knowledge of hepatic diseases and of systemic diseases with hepatic involvement. In addition, liver biopsy has become a valuable tool in solving difficult clinical diagnostic problems.

Diagnosis of tuberculosis has been established by means of liver biopsy on numerous occasions.\(^1\)\(^4\) The extent of hepatic involvement in pulmonary tuberculosis has been studied from post mortem material\(^6\) and recently from specimens obtained by needle biopsy.\(^6\) To determine the value of liver biopsy in a tuberculosis hospital the results of biopsies on 128 patients were reviewed.

**Materials and Methods**

All patients studied were under observation and/or treatment for tuberculosis at the Oak Forest Tuberculosis Hospital. The average age of the patients studied was 40 years. The youngest was 15 and the oldest 77 years. Ninety-five men and 33 women were studied. In general, the reason for selection of patients for liver biopsy could be divided into six groups:

1. Possible miliary tuberculosis in 32 patients.
4. Specific diagnostic problem in 32.
5. Possible amyloidosis in 8.

The possible miliary group consisted of those clinically suspected of having miliary tuberculosis on the basis of characteristic diffuse nodular lesions on chest x-ray films. Some had tubercle bacilli cultured from bone marrow, and one had extensive cavitary lesions on x-ray film. Biopsy was performed as early as possible, but several had been on treatment for as long as four months prior to biopsy. Patients with pleural effusion were studied in an attempt to prove etiology. Those with extra-pulmonary tuberculosis had positive lymph node biopsies, bone lesions, ischiiorectal abscesses, genitourinary tuberculosis, peritoneal, pericardial, or meningeal lesions. The specific diagnostic group consisted of cases in whom cirrhosis was suspected because of abnormal results of liver function tests or with unexplained hepatomegaly. When amyloidosis

---

From the Oak Forest Tuberculosis Hospital and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois.

ACKNOWLEDGEMENTS:

Thanks are due to Dr. Hans Popper for his guidance of this study and for his aid in the interpretation of the histologic findings.
was suspected clinically, a Congo red test and liver biopsy were performed. The last group consists of patients with abnormal results of liver function tests encountered during the course of evaluation of isonicotinic acid hydrazide treatment. These abnormal results raised the possibility of liver damage from the drug, and liver biopsy was performed to further investigate this possibility. Some overlapped into more than one group but were placed under the heading considered most appropriate.

Prothrombin time of 75 per cent of normal or better was required before the biopsy was performed.

During the first half of this study the Silverman needle was used. In the latter half the needle designed by Terry was employed because larger specimens were obtained.

The specimens of liver tissue were fixed in Zenker-formalin solution, cut at four microns, and a single section was stained with hematoxylin and eosin according to established technics. In addition, Mallory’s tri-chrome stain and periodic acid Schiff stains were used in some instances. A series of biochemical determinations, including serum albumin, globulin, tubidometric gamma globulin, cholesterol-cephalin flocculation, thymol turbidity, and alkaline phosphatase were done.

Results

Histologic lesions found were divided into five categories: (1) miliary granulomas; (2) histiocytic nodules; (3) non-specific reactive hepatitis; (4) amyloid infiltration; and (5) non-tuberculous lesions.

The tuberculous granulomas consisted of accumulations of epithelioid cells usually surrounded by a lymphocytic ring. Some Langhans’ type giant cells were present and in some cases central caseation was noted.

FIGURE 1: Miliary granuloma with central caseation and Langhans giant cells in a liver biopsy specimen from a patient with a clinical picture of miliary tuberculosis. Hematoxylin and eosin. (X190)
Tubercles were usually distributed throughout the lobule, but were often seen near the central vein. Tuberculous etiology is suggested by this histologic picture, but cannot be proved on this basis alone. Absolute differentiation from sarcoid follicles cannot be made unless tubercle bacilli are demonstrated by specific staining or culture.

Histiocytic nodules are represented by accumulation of histiocytes apparently differing from Kupffer cells. These endothelial cells resemble epithelioid cells, but as a rule are not as large. Lymphocytes were occasionally found in the nodules. The entire histiocytic nodule is smaller than the tuberculous granuloma and central caseation is not seen. These nodules are strongly suspicious of tuberculous etiology, but are weaker evidence than the tuberculous granuloma described above. In some instances histiocytic nodules were associated with some of the changes described below as non-specific reactive hepatitis (Fig. 2).

Non-specific reactive hepatitis is represented by focal or diffuse degenerative changes of the liver cells, focal necrosis, focal regeneration, Kupffer cell mobilization, and portal and periportal cellular infiltration (Fig. 3). These histologic features vary in intensity and extent in the individual patient. In some instances all of the above changes are present and extensive, and in others only a few of the changes are noted. The extent and severity of histological changes was roughly proportioned to clinical toxicity.

Amyloid changes consisted of deposition of characteristic amyloid material throughout the lobule in varying amounts.

Eight patients were clinically suspected of having secondary amyloidosis.

FIGURE 2: Histiocytic nodule composed of endothelial cells and lymphocytes in a liver biopsy specimen from a patient with far advanced pulmonary tuberculosis. Note also the increase in number and size of the Kupffer cells and the increased cellularity of the portal triads characteristic of non-specific reactive hepatitis. Hematoxylin and eosin. (X95)
Four of these showed extensive amyloid infiltration in the liver (Fig. 4). One with histologic amyloid infiltration had a normal Congo red test. Two who did not have histologic amyloid infiltration had complete removal of Congo red from the serum in one hour.

The non-tuberculous lesions consisted of six instances of fatty infiltration with beginning cirrhosis formation; two cases of viral hepatitis.
and one each of hemochromatosis, myeloid metaplasia, lymphoma and sarcoidosis (Fig. 5).

The most frequently seen lesion was non-specific reactive hepatitis (44 per cent). Next in order of frequency were histiocytic nodules (20 per cent); tuberculous granuloma (19 per cent); specific non-tuberculous lesions (10 per cent); amyloid infiltration (4 per cent); and normal liver (3 per cent). The distribution of histological lesions for each clinical reason for biopsy is presented in Table I.

### TABLE I

<table>
<thead>
<tr>
<th>Reason for Biopsy</th>
<th>No. of Cases</th>
<th>Tuberculous Granuloma</th>
<th>Histiocytic Nodules</th>
<th>Non-Specific Reactive Hepatitis</th>
<th>Amyloid</th>
<th>Normal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible Miliary TBC</td>
<td>32</td>
<td>34</td>
<td>16</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>13</td>
<td>15</td>
<td>23</td>
<td>46</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Extra-Pulmonary TBC</td>
<td>22</td>
<td>40</td>
<td>23</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>32</td>
<td>3</td>
<td>18</td>
<td>37</td>
<td>0</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Possible Amyloid</td>
<td>8</td>
<td>0</td>
<td>12</td>
<td>25</td>
<td>63</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Evaluation</td>
<td>% Drug Effect</td>
<td>21</td>
<td>0</td>
<td>19</td>
<td>71</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| | 23% | 26% | 58% | 5% | 4% | 12% |

FIGURE 5: Partially hyalinized follicle of sarcoidosis in a liver biopsy specimen from a patient with diffuse nodular shadows seen in a chest x-ray film. Hematoxylin and eosin. (X190)
Table II contains the clinical reason for biopsy and extent of pulmonary and extra-pulmonary tuberculosis in each of the 23 cases in which tuberculous granuloma were found.

Table III represents the correlation between the histological diagnosis and the abnormal blood chemistry determinations.

Discussion

The primary objective of this study was to demonstrate the practical value of needle biopsy of the liver in the management of tuberculosis. Tuberculous granulomas in liver tissue means hematogenous dissemination, at least to the liver. Some patients presented the clinical and roentgenologic picture of acute miliary tuberculosis, while others did not. Still others had clinical and roentgenologic evidence of acute miliary tuberculosis, but no tuberculous granuloma was found. Failure to find granulomas may be due to uneven distribution or fewer granulomas, or it may be due to failure to make serial sections of the entire biopsy specimens. The amount of liver tissue obtained is small in comparison to the size of the liver, and tuberculous granulomas may be present in the liver even though not seen on a single section of the biopsy.

Tuberculous granulomas are not necessarily diagnostic of acute miliary tuberculosis, but are frequently seen in extra-pulmonary tuberculosis and tuberculous pleural effusion. From a clinical standpoint, the demonstration of tuberculous granulomas is significant regardless of the diagnosis before biopsy. In some instances of pleural effusion, this was the only laboratory proof of tuberculosis. Some cases of tuberculous lymphadenopathy might not have been adequately treated unless the extent of the tuberculous process had been demonstrated by liver biopsy.

The findings of non-specific reactive hepatitis solved many puzzling clinical and biochemical problems. In several patients a clinical diagnosis of cirrhosis was made but non-specific reactive hepatitis was found. This lesion probably represents a hepatic reaction to tissue breakdown or some other endogenous toxin. The possibility of liver damage from

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>CLINICAL DATA IN 23 PATIENTS WITH TUBERCULOUS GRANULOMAS OF THE LIVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Tuberculosis</td>
<td>Extrapulmonary Tuberculosis</td>
</tr>
<tr>
<td>Reason for Biopsy</td>
<td>No. of Cases</td>
</tr>
<tr>
<td><strong>Milliary TBC</strong></td>
<td>11</td>
</tr>
<tr>
<td><strong>Pleural Effusion</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Extrapulmonary Tuberculosis</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>Hepatomegaly</strong></td>
<td>1</td>
</tr>
</tbody>
</table>
isonicotinic acid hydrazide arose, but non-specific reactive hepatitis was found to account for the clinical and biochemical abnormalities. The severity of the hepatic changes roughly mirrored the systemic toxicity of the disease, and in some patients on isonicotinic acid hydrazide serial biopsies revealed improvement in the histologic appearance.

Liver biopsy proved valuable in establishing the diagnosis of beginning cirrhosis or healing hepatitis, as well as the isolated cases of hemochromatosis, myeloid metaplasia, lymphoma, and sarcoidosis. Each of these patients presented a clinical diagnostic problem that was solved by liver biopsy.

A disparity between the Congo red test and the histological demonstration of amyloid deposition occurred in patients with amyloidosis. Some had abnormal Congo red removal, but no amyloid infiltration was seen. This may mean that the liver is not uniformly involved in secondary amyloidosis.

It was not possible to predict the histologic diagnosis from biochemical abnormalities. These tests are of distinct value in the study of pulmonary tuberculosis but can not be used as a substitute for liver histologic examination. Elevated gamma globulin was the most frequently demonstrated abnormality and the group with tuberculous granulomas had the highest over-all incidence of abnormalities. This had previously been related both to changes in the liver and to the number of plasma cells in bone marrow. Results of the other hepatic tests were not correlated with either clinical findings or with histologic alterations.

SUMMARY

The practical value of liver biopsy in a tuberculosis hospital was found to be:

1. Hematogenous dissemination with or without the clinical features of miliary tuberculosis is recognized. Hepatic dissemination does not neces-
sarily imply generalized miliary tuberculosis which therefore cannot be diagnosed from the liver biopsy specimen alone. Recognition of dissemination is important for prognosis and therapy in pulmonary tuberculosis and more so in extra-pulmonary forms.

2. The degree of non-specific reactive hepatitis (liver damage, focal necrosis and inflammation) reflects systemic toxicity.

3. Frequently associated diseases such as cirrhosis or hepatitis are detected.

4. The presence and extent of amyloid deposition can be evaluated more effectively than with Congo red tests alone.

RESUMEN

El valor práctico de la biopsia del hígado en un hospital de tuberculosis se encontró ser:

1. La diseminación hematogena con o sin las características clínicas de la tuberculosis miliar, se reconoce.
   La diseminación hepática no implica necesariamente la tuberculosis miliar generalizada el cual no puede ser diagnosticada solamente por el espéctmen de la biopsia de hígado.
   El reconocimiento de la diseminación es importante para el pronóstico y el tratamiento de la tuberculosis pulmonar y más aún para la extrapulmonar.

2. El grado de hepatitis reactive no específica (daño hepático, necrosis focal e inflamación) refleja la toxicidad general.

3. Frecuentemente se descubren afecciones asociadas tales como la cirrosis y la hepatitis.

4. La presencia y la extensión de los depósitos amiloïdes puede apreciarse mejor que con la prueba del Congo Rojo sola.

RESUME

Les auteurs démontrent la valeur pratique de la biopsie du foie dans un hôpital pour tuberculeux:

1. Elle permet de reconnaître la disémination hématogène avec ou sans les caractéristiques cliniques de la tuberculose miliare. La dissémination hépatique n'implique pas forcément la tuberculose miliare généralisée, qui ne peut être diagnostiquée sur la seule biopsie du foie. La constatation de la dissémination est importante pour le pronostic et la thérapeutique en tuberculose pulmonaire et plus encore dans les formes extrapulmonaires.

2. Le degré d'une réaction hépatique non spécifique (lésions du foie, foyer de nécrose, et inflammation) reflète une atteinte toxique de ce viscére.

3. Des maladies fréquemment associées, telles que cirrhose et hépatite peuvent être mises en évidence.

4. La présence et l'extension d'une dégénérescence amyloïde peuvent être évaluées avec plus d'efficacité que par les seuls tests au rouge Congo.
ZUSAMMENFASSUNG

Der praktische Wert einer Leber-Biopsie in einem Tuberkulose-Krankenhaus ergab sich in folgendem:


2. Der Grad der unspezifischen reaktiven Hepatitis (Leberschaden, Herdnecrose und Entzündung) spiegelt die allgemeine Toxizität wieder.

3. Oft werden Begleitkrankheiten wie Zirrhose oder Hepatitis entdeckt.


REFERENCES