HISTOLOGIC LIVER ABNORMALITIES IN AN AUTOPSY SERIES OF PATIENTS WITH RHEUMATOID ARTHRITIS

E. M. RUDERMAN,*† J. M. CRAWFORD,‡ A. MAIER,* J. J. LIU,‡ E. M. GRAVALLESE*§ and M. E. WEINBLATT*

*Departments of Medicine and †Pathology, Brigham and Women’s Hospital, and §Department of Cancer Biology, Harvard School of Public Health, Boston, MA 02115, USA

SUMMARY

A retrospective review was performed on 188 autopsied cases of rheumatoid arthritis at our institutions during 1958–1985, prior to the widespread use of methotrexate. Hepatic histology was reported in 182 cases. All available microscopic liver slides from cases in which the autopsy report described portal tract inflammation, fibrosis, cirrhosis, tumour, amyloid, vasculitis, or infections involving the liver were examined and graded by a hepatic pathologist blinded to the original diagnosis, along with a representative sample of cases with reports describing fatty change or no hepatic pathologic abnormalities. Ninety normal and abnormal cases were reviewed from the 182 for which hepatic histology was available. Fifteen cases of diffuse fibrosis were identified upon blinded review. Two cases were graded as severe fibrosis (grades 3 or 4 on a scale of 0–4) without an identifiable pathologic cause, in both of which the liver disease was suspected premortem (alcohol abuse and viral hepatitis). Although the incidence of fibrosis in this series is slightly higher than that previously described, serious fibrotic liver disease was rare. These results support the current practice of limiting pre-treatment liver biopsies prior to methotrexate therapy to patients with suspected liver disease.

KEY WORDS: Rheumatoid arthritis, Liver, Cirrhosis, Autopsy.

PATIENTS with rheumatoid arthritis (RA) have been reported to develop biochemical evidence of hepatocellular dysfunction as well as histologic liver abnormalities [1, 2]. With the increasing use of methotrexate for RA, there has been renewed interest in the baseline pathology of the liver in patients with RA. In particular, there has been concern as to the extent to which RA itself might contribute to the histopathologic changes seen in the liver biopsies of patients treated with methotrexate [3].

In this study, hepatic pathology was examined in a large, unselected series of RA patients. Autopsy reports were reviewed in 188 RA patients autopsied at our institution during the period from 1958 to 1985, prior to the widespread use of methotrexate. Histologic liver abnormalities were common; however, serious, unsuspected liver disease, including cirrhosis, was rare.

PATIENTS AND METHODS

Cases were identified retrospectively from autopsy records of the Peter Bent Brigham, Robert Breck Brigham, and Brigham and Women’s Hospitals. Autopsy reports for the years 1958–1985 were screened for the diagnosis of RA. Clinical charts were reviewed to ensure that all included cases met the 1958 ARA criteria for definite or classical RA. This case definition was chosen instead of current ACR criteria because of the higher likelihood of finding the appropriate inclusion criteria in the older clinical records. One hundred and eighty-eight cases met these criteria. Hepatic histology was described in the autopsy report in 182 cases. In the 182 cases for which hepatic histology was available, the mean age at death was 65.7 yr (range 24–90 yr). The mean duration of disease in these cases was 16.1 yr (range 1–53 yr). One hundred and sixteen cases were female, 126 were rheumatoid factor positive and 80 had rheumatoid nodules. Only one patient had been treated with methotrexate. This patient was not among the 182 cases in which hepatic histology was described and was therefore excluded from further analysis.

Available slides were reviewed in a blinded fashion by a hepatic pathologist (JMC). In nearly all cases, slides were stained only with haematoxylin and eosin (H & E); trichrome and reticulin stains were available on occasion. Tissue histology was scored as previously described [4, 5], using a scale of 0–4 for each of 11 pathologic findings: fatty change, fibrosis, portal tract inflammation, disruption of the limiting plate (spillover of portal tract inflammation into parenchyma), parenchymal hepatocellular necrosis, congestion, lipofuscin deposition, sinusoidal reticulocytosis (mononuclear cells in the sinusoids), granuloma formation, cholestasis in bile ducts or parenchyma, and bile duct proliferation. For each specific finding, a pathologic grade of 0 denoted normal tissue, 1 corresponded to mild pathologic changes, 2 was moderate, 3 was severe, and 4 denoted the most severe example of the given finding. For the specific finding of fibrosis, a grade of 1 corresponded to the presence of any fibrosis, 2 denoted parenchymal extension of fibrosis, 3 denoted portal-to-portal, portal-to-central or central-to-central bridging fibrosis, and a grade of 4 was reserved for...
TABLE I  
Recorded final autopsy diagnoses for 182 cases of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Reported hepatic histology</th>
<th>No. of cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal liver parenchyma</td>
<td>15</td>
</tr>
<tr>
<td>Congestion</td>
<td>112</td>
</tr>
<tr>
<td>Fatty change</td>
<td>42</td>
</tr>
<tr>
<td>Portal tract inflammation</td>
<td>30</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>21</td>
</tr>
<tr>
<td>Tumour</td>
<td>15</td>
</tr>
<tr>
<td>Amyloid</td>
<td>9</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>2</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>2</td>
</tr>
<tr>
<td>Other infections</td>
<td>3</td>
</tr>
</tbody>
</table>

*In some autopsies, more than one finding was described.

septal fibrosis with nodule formation consistent with cirrhosis.

Intra-observer variability in grading was evaluated by randomly selecting 11 cases to be reviewed on two separate occasions. These cases were read several months apart, without knowledge of prior scoring. The overall agreement between values assigned at each occasion for the 11 parameters was 80%. No difference in any finding, including fibrosis, was greater than a single grade.

RESULTS

The recorded final pathologic diagnoses in the 182 cases for which hepatic pathology was described are listed in Table I. All available slides from autopsies describing the significant histologic findings of portal tract inflammation, fibrosis or cirrhosis were reviewed by a hepatic pathologist (JMC) blinded to the original autopsy diagnosis. Slides from 44 of 54 autopsies describing these findings were available for review (81.5%), including all five cases of reported cirrhosis. Available cases (27 of 36) described as tumour, amyloid, vasculitis or liver infection were also reviewed. A total of 66 significantly abnormal cases were reviewed; in some cases, more than one pathologic finding was described at autopsy.

Fifty-two of the 66 abnormal cases subjected to blinded review were identified as having portal tract inflammation (Table II, Fig. 1). In 44 cases, this inflammation was read as grade 1, in six cases it was read as grade 2, and in two cases it was read as grade 4. In both of the latter cases, the inflammation was seen in association with tumour. Eighteen of the 66 abnormal cases were read as fibrosis on blinded review (Table II, Fig. 2). In three instances (two grade 1 and

TABLE II  
Portal tract inflammation and fibrosis seen on blinded pathological review of 90 normal and abnormal autopsy cases

<table>
<thead>
<tr>
<th>Histologic grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal autopsy cases (66)</td>
<td>14</td>
<td>44</td>
<td>6</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Portal tract inflammation</td>
<td>48</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fibrosis with identifiable cause</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

| Normal autopsy cases (24) | 13 | 11 | – | – | – |
| Portal tract inflammation | 22 | 2 | – | – | – |
one grade 3), the fibrosis was seen in association with
tumour involving the liver. In one case, grade 3 fibrosis
was localized to the liver capsule and was associated
with a ruptured peptic ulcer with resultant peritonitis.
In a fifth case, the fibrosis was related to fulminant viral
hepatitis. Thus, excluding cases of hepatic fibrosis of
known cause, a total of 13 cases of diffuse hepatic
fibrosis were identified among the abnormal cases
reviewed; eight cases were assigned a grade of 1, three
cases a grade of 2, one case a grade of 3 (bridging
fibrosis), and one case was assigned a grade of 4
(fibrosis with nodule formation), consistent with
cirrhosis.

Five cases of cirrhosis had been reported at autopsy.
One case had grade 3 fibrosis confirmed on blinded
review, which was associated with a tumour; one case
had grade 2 fibrosis on review; and in one no fibrosis
was seen. In the two autopsy cases of cirrhosis in which
blinded pathologic review confirmed diffuse fibrosis
of grade 3 or 4, a diagnosis of cirrhosis had been
suspected premortem. The liver disease was presumed
to be due to alcohol abuse in one case and to viral
hepatitis in the other. In one additional autopsy report
reviewed, a diagnosis of cirrhosis was made on gross
examination only, and no slides were made for
histological examination. The presence of liver disease
had been suspected premortem in this case, and was felt
to be secondary to alcohol abuse.

The majority of the autopsy reports reviewed had
either fatty change (24 cases) or passive congestion (44
cases) listed as their most significant hepatic finding. In
15 cases, no abnormal hepatic histology was seen on
the original autopsy. In order to verify that the more
significant findings of fibrosis or portal tract inflam-
mation were not missed at autopsy, 24 cases described
as normal or showing only these relatively benign
histologic abnormalities were submitted along with the
abnormal cases for blinded pathological review. In 11
of these cases, blinded review found grade 1 portal tract
inflammation that had been missed at the original
autopsy. Two additional cases had grade 1 fibrosis.
None of the cases reviewed had more severe fibrosis.
Thus, a total of 20 cases from the original 182 autopsy
reports in which hepatic histology was described were
found to have fibrosis upon blinded review of
microscope slides, although in five of these cases a
cause for the fibrosis was identified, leaving 15 cases of
diffuse fibrosis with no identifiable cause (8.2%).

For both normal and abnormal cases from the
original autopsy reports, parameters other than
fibrosis, portal tract inflammation and fatty change
(e.g. granulomas, lipofuscin deposition) were most
commonly graded as zero on review. One definite and
two possible cases of nodular regenerative hyperplasia
were seen among the slides examined [6]. The
availability of slides stained only with H&E made
confirmation of this diagnosis difficult.

DISCUSSION

The goal of this study was to ascertain the frequency
of hepatic cirrhosis and fibrosis in RA patients
autopsied prior to the widespread use of methotrexate.
All available cases reported at autopsy to have
significant histological liver abnormalities, along with
a random sample of cases reported as normal or
showing only fatty change, were reviewed by a hepatic
pathologist blinded to the original diagnosis. Fibrosis
of varying severity was found in 20 cases, in five of
which specific causes for the fibrosis (e.g. tumour,
peritonitis) were identified.

Of the 15 remaining cases of diffuse fibrosis identified
by blinded review, 10 had only mild fibrosis confined
to the portal area, three had parenchymal extension of
fibrosis, one had bridging fibrosis, and only one had
cirrhosis with nodule formation. Of interest is the fact
that the pattern of fibrosis in all cases was periportal,
with or without extension into the liver parenchyma.
This pattern is similar to that described in idiopathic
portal hypertension [7] and has previously been noted
in RA [1, 8, 9]. For the two most severe cases, clinical
data suggested a viral aetiology in one and an alcoholic
aetiology in the other. In an additional autopsy case in
which a diagnosis of cirrhosis was made on gross
examination only, without histological confirmation,
the liver disease was also suspected premortem.

Previous studies have described hepatic histopatho-
logy ranging from mild fatty infiltration to frank
cirrhosis in RA patients. An early report by Lefkovits
and Farrow [1] described hepatic portal fibrosis in 10
of 15 individuals examined by biopsy or at autopsy, but
later series have not confirmed this high frequency. Rau
et al. [8] reported finding ‘reactive hepatitis’ in 43%
of 117 liver biopsies in patients with RA; portal fibrosis
was reported in 18 patients (15.4%) in this series. Mills
et al. [10] found cirrhosis in one of 31 (3.2%) RA
patients undergoing liver biopsy; this patient was a
known alcoholic. ‘Non-specific reactive changes’,
comprising portal tract inflammation, small foci of
hepatoocyte necrosis and fat-containing hepatocytes,
were seen in 74% of the patients in this study. Aside
from the case of cirrhosis, no fibrosis was reported.
Dietrichson et al. [9] described cirrhosis in one of 26
(3.8%) RA patients; this patient did not drink alcohol,
but had had known non-alcoholic liver disease for 10 yr
(not further described). Slight portal fibrosis was seen
in one of the biopsies from this study.

Pre-treatment liver biopsies in RA patients beginning
methotrexate therapy have also supported the low
incidence of fibrosis and cirrhosis in the disease. In
eight series describing a total of 295 patients, fibrosis
was seen in only 11 patients undergoing pre-treatment
biopsies (4%) and cirrhosis in only one (0.3%) [11].
These studies may underestimate the true incidence
of serious liver disease in RA, as patients with significant
known liver disease would have been excluded from
consideration for methotrexate therapy.

We set out to examine the incidence of clinically
significant liver disease in an unselected population
of autopsied RA patients. One limitation of this study is
that cases were selected retrospectively from an
autopsy registry. The incidence of significant liver
disease may have been different in a comparable group
of living RA patients, or even in the RA patients in whom an autopsy was not performed. This study examined a period during which methotrexate was not widely used for the therapy of RA. However, we did not have sufficient clinical information for these patients to rule out the possibility that other medications or concurrent illnesses may have contributed to hepatic pathology.

Additionally, we were unable to review hepatic histologic slides from all of the autopsied patients in this series. As noted above, slides from 81.5% of the autopsy cases of portal tract inflammation, fibrosis or cirrhosis were available for blinded review. An attempt was made to confirm the accuracy of initial benign autopsy reports by reviewing a random sample of cases in which no hepatic pathology, or fatty change alone, was identified. Only two cases of mild (grade 1) fibrosis limited to the portal area were found. No cases of more significant fibrosis missed at original autopsy were found among all the slides examined.

Our data support the relatively common finding of portal tract inflammation previously described in liver biopsies from RA patients [8, 10, 12]. Fibrosis was identified in 20 of the 182 autopsy cases reviewed (11.0%). In five of these cases, a cause was identified, leaving 15 cases of diffuse fibrosis without an identifiable cause (8.2%), an incidence higher than that previously described. However, severe, intrinsic liver disease (i.e. bridging fibrosis or nodule formation consistent with cirrhosis) was seen in only two patients (1.1%) in whom slides were available for review, and the finding was suspected premortem in both cases. These data confirm that serious fibrotic liver disease is rare in RA, and support the current practice of limiting pre-treatment liver biopsies prior to methotrexate therapy to patients with suspected liver disease.

ACKNOWLEDGEMENTS

These studies were supported in part by NIH grants AI-07306 and AR-07530 (EMR) and DK-39512 (JMC). EMG is the recipient of an Arthritis Foundation Investigator Award.

REFERENCES