Comparison of Sonograms and Liver Histologic Findings in Patients with Chronic Hepatitis C Virus Infection

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Gray scale ultrasonographic images of the liver were correlated with histologic findings in patients with chronic hepatitis C virus infection. The gray scale patterns of 64 livers with chronic hepatitis C virus infection were categorized as normal, fatty, fibrofatty, fibrotic, or inflammatory and were graded as mild, moderate, or severe. Liver biopsy specimens also were analyzed for the presence of fat, inflammation, and fibrosis and graded similarly. No correlation was found between fatty and fibrofatty sonographic findings with any of the three histologic patterns. Correlations were found between fibrotic sonographic findings and both fibrotic and inflammatory histologic findings ($r = 0.27; P = 0.03$). Although some pathologic features of liver disease were detected by ultrasonography, no useful correlation was noted between results of sonography and histologic examination. KEY WORDS: Hepatitis C virus; Liver, ultrasonography; Infection, hepatitis C.

MATERIALS AND METHODS

Over a four year period (1993–1996), 77 patients with chronic HCV infection and a positive anti-HCV antibody test (ELISA-2, Ortho-Diagnostics, Raritan, NJ) underwent percutaneous ultrasonographically

ABBREVIATIONS

HCV, Hepatitis C virus; ALT, Alanine aminotransferase; SD, Standard deviation; ULN, Upper limit of normal

Hepatitis C virus is the most common cause of chronic hepatitis in the United States. In patients with chronic HCV infection, assessments of the severity of inflammatory liver injury (grade) and the degree of hepatic scarring (stage) are used to guide clinical management. Gray scale ultrasonography has been reported to detect histologic features of chronic liver disease. We compared retrospectively the gray scale liver images and histologic results in hepatitis C patients evaluated with sonographically guided liver biopsy to see if any correlation existed between sonographic and biopsy findings. If a positive correlation did exist, ultrasonography could be an important cost-effective means of monitoring the disease in these patients.
guided liver biopsy at our institution. Sixty-four of these patients formed our study population. Ultrasonograms, liver biopsy results, and clinical information were available for this group. All images of the liver were acquired with Acuson XP 10 and 128 units (Acuson, Mountain View, CA) using V4, V328, V3.5, or C366 transducers. Two or three core liver biopsies were obtained from the anterior segment of the right lobe in each patient using an 18 gauge needle (Bard Biopsy or Magnum assembly, C.R. Bard, Covington, GA). Patient age, sex, serum ALT level, sonographic size and texture of the liver, and liver histologic findings were reviewed. Size was determined by standard measurement of cranial to caudal length in the right midaxillary line.

Sonographic images were classified simultaneously by two blinded readers (R.K., G.S.) as having normal, fatty, fibrofatty, fibrotic, or inflammatory patterns. A liver was considered fatty if it demonstrated increased echogenicity, loss of portal venule walls, closely packed echoes, and decreased through-transmission. A liver was considered fibrotic if it demonstrated a coarsened echotexture with a pinhead pattern but with preservation of the diaphragm. A fibrofatty liver had both fibrotic and fatty features. A liver was considered inflammatory if echogenic portal triads were observed in a hypoechoic liver or preservation of portal triads was noted in a background of fatty infiltration. If any features of cirrhosis were present, including an irregular contour or nodularity, the liver disease was graded as severe (3) fibrosis. Grading was otherwise done subjectively for degree of severity of the various ultrasonographic patterns. After the images of the liver were categorized appropriately on the basis of the sonographic pattern, the images within the given category were then graded subjectively on a spectrum as mild (1), moderate (2), or severe (3).

Biopsy specimens were examined blindly for the presence or absence of steatosis, inflammation, and fibrosis and were graded using the method of Desmet and coworkers. Statistical comparison of sonographic patterns with corresponding histologic findings was performed using a Spearman rank correlation coefficient.

Results from a subset of 35 patients with end-stage renal disease or a history of end-stage renal disease and a functioning renal allograft were analyzed separately by a Wilcoxon rank sum test for differences in sonographic and histologic findings. Because biopsy specimens from 12 of these patients were examined by two pathologists (F.S., S.N.T.) separately, the histologic results from these specimens were analyzed for correlation by an intraclass correlation coefficient.

RESULTS

Clinical evaluations, sonograms, and liver biopsy specimens from 64 patients (39 male, 25 female) aged 17 to 67 years (mean, 43.9 ± 11.6 SD; median, 44 years) were analyzed (Figs. 1 to 3). Liver size was 12 to 20.2 cm (mean, 15.2 cm ± 2 SD). ALT values were one to 68 times the ULN (which equaled 40 units) with a mean of 2.9 times the ULN and a median of one times the ULN (54.8%). Thirty-five patients had end-stage renal disease, four had a history of alcohol abuse, two had biopsy-proved cirrhosis, and one had congestive heart failure. Two patients had ascites;

Figure 1 A, Normal liver. Longitudinal ultrasonogram of the right lobe of the liver. Pathologic findings normal. B, Ultrasonogram: normal; pathologic findings: mild inflammation, mild fibrosis.
none had hepatoma. No significant clinical history was present in the remaining 22 patients.

Correlation was found between abnormal serum levels and histologic inflammation \((r = 0.3, P < 0.01)\) in study patients. Ultrasonographic and histologic findings are presented in Table 1. Note that no sonographic categories were considered inflammatory. No correlation was found between the fatty or fibrofatty patterns on ultrasonography and the histologic findings of steatosis, fibrosis, or inflammation. However, a correlation was found between the fibrotic pattern on ultrasonography and the presence of fibrosis and inflammation at histologic examination \((r = 0.27, P = 0.03)\). In addition, no correlation was noted between grade of fibrosis on ultrasonography and grade of fibrosis on histologic examination. An inverse correlation was observed between increasing liver size and fibrotic pattern on ultrasonography \((r = 0.33, P < 0.01)\). This is expected since the liver shrinks as it becomes increasingly fibrotic or cirrhotic. A similar correlation could not be made between liver size and the presence of fibrosis at histologic examination. The reason for this lack of correlation remains unclear, but it may be due to sampling error. In the subset of 35 patients with end-stage renal disease, no additional correlation between sonographic findings and histologic findings was present. In the group of 12 patients in whom the biopsy specimens were examined by two pathologists separately, poor interobserver correlation was noted in grading of inflammation and fibrosis (Table 2).

Figure 2 A, Ultrasonogram: Mild fatty liver, some loss of portal venule walls, but preservation of diaphragm. Pathologic findings: Moderate inflammation, mild fibrosis, no steatosis. B, Ultrasonogram: Moderate fatty liver, loss of portal venule walls, tightly packed echoes, and some loss of diaphragm. Pathologic findings: Mild inflammation, mild fibrosis, mild steatosis.
but potentially reversible process that may resolve
without leaving any residual structural abnormality.

Two limitations of this study are that it was a re-
verspective study, and prospective liver evaluation
during scanning would likely allow for more accu-
rate parenchymal analysis. Over the 4 year period of
data accumulation, equipment and transducers
improved, with superior imaging of the liver being
possible in the more recent cases.

Nevertheless, this study demonstrates that, at the
present time, gray scale ultrasonography cannot be
used as a method of grading or staging chronic HCV
infection, and, by inference, other inflammatory liver
diseases with the same histologic abnormalities.
Appropriate management of HCV infection requires
accurate grading and staging; chronic inflammation
with only minimal fibrosis and small amounts of
hepatic iron favors a good response to therapy with
alpha-interferon 2. Biopsy is equally important in the
care of patients with other inflammatory liver dis-
ases, many of which cannot be diagnosed accu-
rately without examination of a liver biopsy
specimen.

A correlation was found between elevated serum
ALT levels and the presence of inflammation on his-
tologic examination. This finding is consistent with
the results of other studies, although it is considered
to be unreliable by hepatologists, as active disease
can be found in patients with low or normal ALT
levels.

It is widely recognized that some variation will
occur in interpretation of liver biopsy findings from
observer to observer. This was certainly demon-
strated in the 12 biopsy specimens that were evalu-
ated by the two pathologists in our study (Table 2). A
sampling error of up to 10% is accepted for liver
biopsies in some diseases.4 This fact and the findings
in our study do raise some concern regarding use of
pathologic findings as the gold standard.

Since a large portion of our study population had
end-stage renal disease, we examined this group as a
subset to determine if they had any unique charac-
teristics. Previous studies have shown that HCV
infection is not made worse by hemodialysis or
renal transplantation and associated immuno-
suppression.10 Findings in the subset of patients with
end-stage renal disease evaluated in our study were
not different from those in the rest of the study pop-
ulation. Slightly more fat was detected by ultra-
sonography and biopsy in these patients, a finding
that might be related to chronic immunosuppressive
therapy with prednisone.

<table>
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<tr>
<th>Table 1: Comparison of Sonographic Pattern with Histologic Pattern</th>
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<tr>
<td>Ultrasound Pattern (n)</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Normal (14)</td>
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<tr>
<td>(5–0–0)</td>
</tr>
<tr>
<td>Fatty (6)</td>
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<td>(2–2–0)</td>
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<tr>
<td>Fibrofatty (16)</td>
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<td>(6–2–2)</td>
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<td>Fibrotic (28)</td>
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<td>(10–3–0)</td>
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In conclusion, although microscopic features of liver disease in patients with chronic HCV infection were detected by ultrasonography, no consistent correlation between sonographic and histologic findings was found, suggesting that ultrasonographic imaging is unreliable for grading and staging the degree of liver damage in chronic HCV infection.

**REFERENCES**


**Table 2: Interobserver Variation of Histologic Interpretation in 12 Patients After Double Reading**

| ICC* Path (I) = –0.07 | Very poor |
| ICC Path (F) = 0.21  | Not correlative |
| ICC Path (S) = 0.78 P < 0.001 | Very high |

*Intraclass correlation coefficient.
I, Inflammation; F, fibrosis; S, fat.