Alcoholic Liver Disease: Clinical and Sonographic Features

Sien-Sing Yang*

Alcoholism is a worldwide public health problem. Ethanol abuse is not uncommon among those with chronic viral hepatitis in the Asia-Pacific region. In patients with chronic hepatitis B and C, the occurrence of alcoholism may increase viral replication and exacerbate liver injury, which results in the progression of chronic viral hepatitis to liver failure, cirrhosis and hepatocellular carcinoma. The clinical features and the role of sonography in the diagnosis of alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis are reviewed. The differential diagnosis between different alcoholic liver diseases and viral hepatitis are discussed.

KEY WORDS — alcoholic liver disease, diagnosis, sonography

Introduction

The Asia-Pacific region has a high prevalence of viral hepatitis and hepatocellular carcinoma [1,2]. Economic progress has led to increased ethanol consumption and changes in drinking behavior [3,4], which have resulted in an increased number of cases of alcoholic liver disease in Taiwan. Ethanol abuse is not uncommon among those with chronic viral hepatitis. Alcoholism may increase viral replication and exacerbate liver injury, which results in the progression of chronic viral hepatitis to liver failure, cirrhosis and hepatocellular carcinoma [5–7]. In alcoholic liver disease, diminished food intake and morphologic and functional alterations in intestinal mucosa cause malnutrition [8,9]. Malnutrition aggravates alcoholic liver disease and increases mortality [10]. Depression has a more immediate mortality risk among men with alcoholism [11]. Alcoholism is a worldwide public health problem.

Pathogenesis

In viral hepatitis B and C, liver injuries are mainly caused by cellular immune responses against infected hepatocytes [12]. In viral hepatitis, the histologic features include lymphocytes around hepatocellular necrosis, portal inflammation, piecemeal necrosis, and portal fibrosis [13]. Different from viral hepatitis, the liver injuries in alcoholic liver disease consist of oxidative stress-related hepatocellular necrosis and stellate cell-related fibrogenesis [14,15].
Damage caused by free radicals and lipid peroxidation lead to ballooning changes in hepatocytes and the formation of Mallory bodies. Mallory bodies are folded and unfolded proteins in response to oxidative stress; Mallory bodies consist of abnormal keratins, ubiquitin, heat shock proteins, and the protein p62 [16]. Tumor necrosis factor-α induces the formation of proinflammatory cytokines, which cause chemotaxis and aggregation of polymorphonuclear leukocytes around the ballooning hepatocytes [17]. Ethanol-induced hypoxia, lipid peroxidation and acetaldehyde activate the stellate cells to increase matrix production and fibrogenesis [18–20].

Clinical Features

The clinical classification of alcoholic liver disease is based on the pathologic findings of fatty liver, alcoholic hepatitis and alcoholic cirrhosis [21]. Fatty liver is also found in patients with alcoholic hepatitis and alcoholic cirrhosis. A clinical attack of acute alcoholic hepatitis can occur in patients with alcoholic cirrhosis.

Fatty liver

Fatty liver is the most common morphologic change in alcoholic liver disease. Nicotinamide adenine dinucleotide (NADH), a metabolite of ethanol generated under alcohol dehydrogenase, causes increased formation of fatty acids and decreased oxidation of fatty acids [22]. Acetaldehyde, another metabolite of the alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1) pathways, may cause mitochondrial dysfunction [23].

Alcoholic fatty liver is often asymptomatic. Alcoholic liver disease is evident only after identification of hepatomegaly. Alcoholic fatty liver is reversible following abstinence from ethanol abuse. Mildly abnormal aminotransferases and bilirubin levels are often found in patients with alcoholic steatosis [24]. The elevated indirect bilirubin levels reflect hemolysis. Zieve syndrome is characterized by an acute metabolic condition following withdrawal from prolonged alcohol abuse, and includes hemolytic anemia, hyperlipoproteinemia, jaundice, and abdominal pain [25]. Aspartate aminotransferase (AST) levels are usually higher than alanine aminotransferase (ALT) levels, with a high AST/ALT ratio of greater than 2 [26]. The AST and ALT levels are often less than 300 IU/L. The glutamyl transpeptidase levels are often elevated. Patients with alcoholic steatosis may develop hypertriglyceridemia and macrocytosis with increased mean cell volume. Desialylated ferritin (carbohydrate-deficient transferrin) is formed by the reduced attachment of carbohydrate moieties to transferrin in patients with prolonged heavy alcohol consumption [27]. Carbohydrate-deficient transferrin is a sensitive and specific marker for alcohol abuse.

Liver biopsy is the most sensitive and specific method for evaluating the degree of hepatic injury and fibrosis to help therapeutic decision making [28,29]. The fatty change is mainly macrovesicular at zone 2 and 3 [30]. Macrovesicular fatty change is the accumulation of triglycerides within the cytoplasm of hepatocytes which displace the nuclei. Mitochondrial dysfunction leads to the enlargement of mitochondria, known as megamitochondria, and ballooning of hepatocytes [31]. Perivenular and sinusoidal fibrosis are the thin intraluminal fibrosis in terminal hepatic venules and surrounding sinusoids [32,33]. Perivenular and sinusoidal fibrosis can be found in patients with alcoholic fatty liver, and a small number of Mallory bodies are often found in the perivenular zone.

The sonographic features of alcoholic fatty liver are hepatomegaly, increased echogenicity, vascular blurring, loss of diaphragm definition, and deep attenuation [34,35]. Thickened abdominal wall and liver fibrosis may generate sonographic features of “bright liver pattern” similar to those of hepatic steatosis [36,37]. Comparing brightness of liver to brightness of renal cortex (liver–kidney contrast) and spleen are widely used to exclude the influence of hepatic fibrosis [38–40]. The subjective assessment of fatty liver on sonography has substantial observer variability [41].

Sonographic findings of focal fat deposition or sparing are not uncommon in fatty liver. Focal fat
deposition or sparing usually occurs in the porta hepatis, gallbladder fossa, subcapsular region, and medial segment adjacent to the falciform ligament or ligamentum venosum [42,43]. The contour of a liver tumor is usually round or oval. In contrast, the shape of a fatty pseudolesion is often geographic. Fatty pseudolesions have poorly delineated margins and do not have mass effects on vessels and other structures [42,43]. Color Doppler sonography and contrast agents are useful for the differential diagnosis of pseudolesions [44,45].

The fatty liver index is calculated by the equation: 1.03×AST (IU/L) + 0.152×triglyceride (mg%) − 49.75×Doppler perfusion index [46]. The Doppler perfusion index is the ratio of hepatic arterial to total liver blood flow [46]. The fatty liver index has been suggested to be a simple and accurate predictor of hepatic steatosis [47].

The hepatic artery resistive index is calculated by the equation: (peak systolic value − end diastolic value)/peak systolic value [48]. Patients with fatty liver have a higher hepatic artery resistive index due to an increased intrahepatic resistance, which can be reversed by metformin treatment [49,50]. Patients with fatty liver may also develop abnormal biphasic or monophasic hepatic vein waveform patterns [51].

**Alcoholic hepatitis**

Patients with alcoholic hepatitis demonstrate a wide range of clinical features, from asymptomatic to severe jaundice, ascites, prolonged prothrombin time, encephalopathy, and hepatorenal failure in full-blown cases [52–54]. Patients with alcoholic hepatitis often have marked hepatomegaly (weight, >3,000 g), leukocytosis (rarely >10,000/mm³) and a mild degree of fever (usually <37.5°C). A serum AST/ALT ratio of >2.0 is often used in the diagnosis of alcoholic hepatitis. Alternative diagnoses should be considered in patients with high serum AST and ALT levels (>400 IU/L) [55]. Hepatic systolic bruits are regarded as a sign of increased hepatic arterial flow [56]. Patients with alcoholic hepatitis and a discriminant function of >32 have a poor prognosis [57]. Discriminant function is calculated by the equation: (4.6×prothrombin time above control in seconds) + serum bilirubin. The mortality rate of alcoholic hepatitis has been considerably improved by the use of corticosteroids [57], and the complication of hepatorenal syndrome is reduced by pentoxyphylline [58].

Alcoholic hepatitis shows marked ballooning degeneration of hepatocytes and Mallory bodies with polymorphonuclear leukocyte infiltration mainly in the perivenular zone [59–61]. The occurrence of perivenular and sinusoidal fibrosis is often extensive. The presence of macrovesicular fatty change and cholestasis are prominent but not essential for diagnosis.

The clinical features of nonalcoholic steatohepatitis are similar to those of alcoholic hepatitis (Table 1). Patients with alcoholic hepatitis usually have higher serum bilirubin levels and AST/ALT ratios of >2, whereas nonalcoholic steatohepatitis patients often have ratios of <2 [62,63]. Alcoholic hepatitis patients usually have a higher number of Mallory bodies and a greater degree of perisinusoidal fibrosis than patients with nonalcoholic steatohepatitis. Polymorphonuclear leukocyte infiltration in the perivenular zone and portal area is uncommon in nonalcoholic steatohepatitis. Glycogenated nuclei can be found in patients with nonalcoholic steatohepatitis [64].

| Table 1. Clinical features of nonalcoholic steatohepatitis and alcoholic hepatitis |
|---------------------------------|-----------------|-----------------|
|                                 | Nonalcoholic steatohepatitis | Alcoholic hepatitis |
| Malnutrition                    | +                             | ++ or +++        |
| Hepatomegaly                    | + or ++                       | ++ or +++        |
| Jaundice                        | +                             | ++ or +++        |
| AST/ALT ratio                   | <2                            | >2              |
| Histology                       |                               |                 |
| Mallory bodies                  | +                             | ++ or +++        |
| Sinusoidal fibrosis             | +                             | ++ or +++        |
| PMN infiltration                | +                             | ++ or +++        |
| Glycogenated nuclei             | +                             | –                |

AST = aspartate aminotransferase; ALT = alanine aminotransferase; PMN = polymorphonuclear leukocytes.
The clinical features of severe alcoholic hepatitis presenting with fever, jaundice and abdominal pain are often confused with those of acute cholecystitis or biliary infection [65]. The differential diagnosis of alcoholic hepatitis is clinically important. Acute cholecystitis patients require surgery, while alcoholic hepatitis patients face a high rate of mortality following surgery.

Fulminant and subfulminant hepatic failure caused by viral hepatitis B are not uncommon in Taiwan [66,67]. A viral hepatitis B infection can be identified by any positive serum markers including hepatitis B surface antigen and hepatitis B virus deoxyribonucleic acid. Fulminant and subfulminant hepatic failure are characterized by a shorter clinical course (weeks vs. months), smaller liver size, AST/ALT ratio of < 1, higher AST and ALT levels of > 400 initially, less fever and less leukocytosis (in those without bacterial infection), and predominant lymphocyte infiltration in comparison to those with alcoholic hepatitis [68,69] (Table 2). Liver histology offers the most accurate diagnosis. In those with both viral hepatitis and alcoholism, the histologic findings have shown characteristics of both viral hepatitis and alcoholic liver disease.

### Table 2. Clinical features of fulminant hepatic failure and alcoholic hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Fulminant hepatic failure</th>
<th>Alcoholic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course</td>
<td>Weeks</td>
<td>Months</td>
</tr>
<tr>
<td>Liver size</td>
<td>Small</td>
<td>Huge</td>
</tr>
<tr>
<td>Fever</td>
<td>+ or −</td>
<td>+</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>+ or −</td>
<td>&lt; 12,000/mm³</td>
</tr>
<tr>
<td>AST:ALT (IU/L)</td>
<td>High initially</td>
<td>&lt; 300 : &lt; 100</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>&lt; 1</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mallory bodies</td>
<td>−</td>
<td>++ or +++</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Bridging</td>
<td>Perivenular/ sinusoidal</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>Lymphocytes</td>
<td>PMN</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase; PMN = polymorphonuclear leukocytes.

Similar to alcoholic fatty liver, sonographic features of alcoholic hepatitis include hepatomegaly and fatty liver. Sonography can identify complications such as the presence of ascites, collaterals and portal hypertension [70–72]. Sonography also helps rule out cholecystitis and biliary infection.

“Dilated hepatic artery” appears in patients with acute alcoholic hepatitis [73]. Dilated hepatic artery is a visible branch of the hepatic artery parallel to the portal vein branch, and has been diagnosed as the pseudoparallel channel sign [73].

The mean hepatic artery diameter and peak systolic velocity are significantly larger in patients with alcoholic hepatitis than in those with cirrhosis; the hepatic artery resistive index is lower in patients with alcoholic hepatitis than in those with cirrhosis and healthy controls [74,75]. An elevated hepatic artery diameter or peak systolic velocity measured by duplex Doppler ultrasound suggests a case of acute alcoholic hepatitis [76]. The progression of alcoholic hepatitis to cirrhosis causes an elevation in hepatic arterial resistive index, indicating that the impairment of arterial responsiveness is a consequence of fibrosis with vascular distortion [77].

### Alcoholic cirrhosis

Similar to alcoholic hepatitis, patients with alcoholic cirrhosis also present with hepatomegaly. The clinical features of alcoholic cirrhosis range from asymptomatic to decompensated liver function with many complications [78]. Patients with alcoholic cirrhosis often have malnutrition, hypertrophic parotid glands, vascular spiders, palmar erythema, hepatomegaly, portal hypertension (collaterals on abdominal wall, ascites, variceal hemorrhage), feminization (gynecomastia and hypogonadism), neuropathy (finger clubbing, Dupuytren’s contractions, and peripheral neuropathy), and encephalopathy [79]. The presence of a firm liver edge is a useful sign of alcoholic cirrhosis [80].

Patients with alcoholic cirrhosis have higher AST and ALT levels, hypoalbinemia, hyperbilirubinemia, anemia, leukocytopenia, thrombocytopenia, and prolonged prothrombin time. Reduced platelet count and function reflect hypersplenism.
Alcoholic cirrhosis is characterized by widespread poorly-defined micronodules (≤ 3 mm diameter) and extensive fibrous septa [81,82]. In patients who have stopped drinking, the nodules become well demarcated and enlarged (macronodular > 3 mm) with thin septa. Active alcoholics may have a variable degree of Mallory bodies, perivenular fibrosis and fatty liver [83]. Cholestasis presents in the advanced stage of alcoholic cirrhosis. Hepatocellular carcinoma may be present in patients with advanced cirrhosis, usually in those who have stopped drinking.

Different from patients with alcoholic hepatitis (Table 3), patients with alcoholic cirrhosis may have abused alcohol for months or years. Fever and leukocytosis are not features of alcoholic cirrhosis. The occurrence of leukocytosis may indicate a bacterial infection. The AST/ALT ratio is often > 2 in both alcoholic cirrhosis and alcoholic hepatitis patients. The hepatic arterial flow is higher in patients with alcoholic hepatitis and audible arterial bruits but lower in alcoholic cirrhosis patients.

In contrast to postnecrotic cirrhosis (Table 4), the liver size in an alcoholic liver cirrhosis patient is significantly enlarged with a mildly uneven liver surface. The liver size in a viral hepatitis patient is postnecrotic with shrinkage of the right liver. The liver surface of a patient with advanced postnecrotic cirrhosis is often macronodular. Splenomegaly is common in postnecrotic cirrhosis but not in alcoholic cirrhosis. The degree of portal hypertension, collaterals, malnutrition and neuropathy in alcoholic cirrhosis patients is usually much more prominent than that in postnecrotic cirrhosis; alcoholic cirrhosis patients have delayed nerve conduction and evoked potentials [84–86]. Unlike patients with postnecrotic cirrhosis, patients with alcoholic cirrhosis can have a variable degree of fatty liver.

Sonographic features of alcoholic cirrhosis include hepatomegaly, bluntness of liver edge, coarseness of liver parenchymal texture, and fatty liver. Irregularity of liver surface, hepatomegaly, and attenuation of the ultrasound beam are the most useful signs for the assessment of cirrhosis [87]. A scoring system for ultrasound features, including edge, surface and parenchymal texture of the liver, has been used for the evaluation of liver fibrosis stage [88,89]. Cirrhosis can be correctly diagnosed in 82–88% of patients with chronic liver disease using a scoring system consisting of 12 clinical and 11 Doppler ultrasonic variables [90].

A decreased portal vein response to respiration suggests the occurrence of portal hypertension [91]. Platelet count to spleen diameter ratios are suggested to predict the presence of esophageal varices in compensated cirrhosis [92]. A left portal vein diameter of equal to or greater than the right portal vein diameter indicates chronic alcoholic liver disease [93]. Reduced portal flow velocity, portal vein diameter of > 13 mm, and the lack of mild caliber variation in the superior mesenteric vein suggest a diagnosis of portal hypertension [94,95]. Hyposplenism is common in alcoholic cirrhosis and less common in nonalcoholic cirrhosis [96].

Postnecrotic cirrhosis shows an undulating surface and shrinkage of the right liver [97]. Therefore, the ratio of transverse caudate lobe width to right lobe width, the ratio of the right lobe to left lobe longitudinal diameter, and undulating liver surface

<table>
<thead>
<tr>
<th>Table 3. Clinical features of alcoholic hepatitis and alcoholic cirrhosis</th>
</tr>
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<tbody>
<tr>
<td>alcohol hepatitis</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Liver size</td>
</tr>
<tr>
<td>Hepatic arterial</td>
</tr>
<tr>
<td>bruit</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Leukocytes</td>
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<td>Platelets</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
|                   | Bridging fibrosis    | –                     | +++

AST = aspartate aminotransferase; ALT = alanine aminotransferase.
are helpful characteristics in assessing postnecrotic cirrhosis [98,99]. They are, however, not helpful in the assessment of alcoholic cirrhosis.

Portal hypertension is one of the major complications of cirrhosis. Noninvasive duplex Doppler ultrasound has been widely utilized in assessing the hemodynamics of the portal system [100]. Recent advances in contrast agent technology and color Doppler sonography in the evaluation of portal hypertension were recently reviewed [101].

In addition to sonography, various methods have been used in the assessment of fibrosis, including serum transaminases, homeostasis model assessment, AST-to-platelet ratio, FibroTest, European Liver Fibrosis panel, liver biopsy, computed tomography, magnetic resonance imaging, transient elastography, and genomic and proteomic techniques [102]. Transient elastography has recently been of interest in the noninvasive assessment of hepatic fibrosis [103,104]. However, recent publications show that liver stiffness in viral hepatitis and cirrhosis may be due to a flare-up of aminotransferases in the absence of hepatic fibrosis [105,106]. The role of transient elastography in the noninvasive assessment of hepatic fibrosis requires further study.

**Table 4. Clinical features of postnecrotic cirrhosis and alcoholic cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>Postnecrotic cirrhosis</th>
<th>Alcoholic cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>+ or ++</td>
<td>++ or +++</td>
</tr>
<tr>
<td>Liver size</td>
<td>Small</td>
<td>Huge</td>
</tr>
<tr>
<td>Liver surface</td>
<td>Macronodular</td>
<td>Micronodular</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>–</td>
<td>+ or –</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>+ or ++</td>
<td>++ or +++</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>+</td>
<td>++ or +++</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>Leukocytopenia</td>
<td>Leukocytopenia</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>1–2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mallory bodies</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Sinusoidal fibrosis</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>Lymphocytes</td>
<td>PMN</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase; PMN = polymorphonuclear leukocytes.

**References**


