

Phenotypes and Pathology of Drug-Induced Liver Disease

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KEYWORDS

• Liver biopsy • Histopathology • Hepatotoxicity • Drug-induced liver injury

KEY POINTS

- Liver tissue has a limited number of morphologic patterns that occur in response to various forms of injury.
- Drug hepatotoxicity can mimic virtually all forms of naturally occurring liver disease.
- Drugs with hepatotoxic potential generally cause recurring patterns of injury that are characteristic for each drug.
- Liver biopsy is often useful in determining whether histologic features characteristic of a particular drug-induced injury are present.

Chemical hepatotoxicity is a well-recognized phenomenon, whereas hepatic injury caused by medications available for therapeutic use is an uncommon but still far from rare occurrence in medical practice.¹⁻⁶ The drug approval process in developed countries keeps most highly toxic agents from reaching the market, so that the frequency of hepatotoxicity from any particular drug is generally less than 1% (usually much less). Nevertheless, there are so many different drugs in use that the aggregate number of cases is appreciable. Furthermore, as discussed elsewhere in this issue, the widespread use of herbal remedies and dietary supplements that are generally not regulated has resulted in numerous instances of toxic hepatic injury for which firm statistical documentation is not available.

CLINICAL SYNDROMES AND HISTOLOGIC CORRELATES

The diagnosis of hepatotoxicity is complicated because drug-induced liver injury is a great imitator, capable of mimicking all types of liver disease from other causes, in

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clinical presentation and pathologic features (**Table 1**). Frequent presentations that bring patients to clinical attention and prompt liver biopsy include the following:

- Asymptomatic liver test abnormalities: routine screening tests detect many cases of mild liver injury in asymptomatic patients who only have liver test abnormalities, usually mildly elevated aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase.
- Acute seronegative viral hepatitis-like illness with anorexia, malaise, elevated transaminases with or without jaundice.
- Cholestatic hepatitis: viral hepatitis-like but with jaundice greater than one would expect from the degree of liver injury.
- Fulminant liver failure: jaundice and very high transaminases followed by hepatic coma over a period of a few days to a few weeks.
- Venous outflow obstruction: usually an acute process with features of fulminant liver failure and with rapidly accumulating ascites.
- Autoimmune hepatitis-like, which may have acute or fulminant presentation or may have an insidious onset with minimum symptoms.

Table 1
Clinical syndromes that can be mimicked by drug-induced liver injury and their pathologic counterparts

Clinical Syndrome	Pathologic Phenotypes
Asymptomatic liver test abnormalities	Adaptive changes Steatosis Phospholipidosis Mild necroinflammatory changes
Acute viral hepatitis-like \pm jaundice	Acute panlobular hepatitis Mononucleosis-like hepatitis Hepatitis with confluent necrosis
Autoimmune hepatitis-like	Autoimmune hepatitis-like with severe injury, plasma cells \pm confluent necrosis and/or fibrosis
Acute liver failure	Submassive or massive lytic necrosis Submassive or massive coagulative necrosis Microvesicular steatosis
Venous outflow obstruction	Hepatic vein thrombosis with severe congestion and necrosis Veno-occlusive disease (sinusoidal obstruction syndrome) Nodular regenerative hyperplasia
Obstructive jaundice-like	Bland cholestasis Cholestasis with mild hepatocellular injury Cholestasis with acute cholangitis
Cholestatic hepatitis	Combined hepatocellular and cholestatic injury \pm cholangitis
Chronic cholestasis	Chronic cholestasis and ductopenia following acute cholestatic injury
Fibrosis and cirrhosis	Cirrhosis \pm hepatitis, steatohepatitis or other liver disease
Noncirrhotic portal hypertension	Nodular regenerative hyperplasia Hepatoportal sclerosis
Liver disease with signs of hypersensitivity and/or disease in other organs	Acute or cholestatic hepatitis \pm confluent necrosis
Primary hepatic neoplasms	Hepatocellular adenoma Hepatocellular carcinoma Hepatic angiosarcoma

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