The Pathology of Acute Liver Failure

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KEYWORDS

• Acute liver failure pathology • Massive hepatic necrosis
• Submassive hepatic necrosis • Zonal necrosis • Acetaminophen
• Hepatotropic viral hepatitis • Autoimmune hepatitis

KEY POINTS

- Acute liver failure is typically characterized pathologically by massive hepatic necrosis with extensive loss of parenchyma, variable inflammation, and bile ductular proliferation.
- Identifying zonal, nonzonal, or hepatitic patterns of submassive hepatic necrosis may help to distinguish the etiology; drug toxicity and hepatotropic viral infection are the most common causes.
- Centrilobular necrosis is the most common zonal pattern of injury, and the one associated with most diverse etiology.
- Determining prognosis based on percent viable remaining hepatic parenchyma in acute liver failure specimens is prone to sampling error owing to regional variation in necrosis and inflammation.
- Owing to the liver's capacity for recovery, regeneration and regenerative nodule formation in specimens from patients with acute liver failure may occur and should be distinguished from cirrhosis.

Acute liver failure (ALF; also called fulminant hepatic failure, fulminant hepatitis, acute hepatic failure) is an uncommon (<10 cases/million persons/year) but severe disease. It is defined by the American Association for the Study of Liver Disease as acute hepatitis in patients with no preexisting liver disease, presenting within 26 weeks of symptom onset with coagulopathy (International Normalized Ratio of $\geq$1.5) and the presence of an altered sensorium (encephalopathy). Fulminant hepatic failure historically described patients with encephalopathy within 8 weeks of symptom onset, and subfulminant hepatic failure described those with encephalopathy developing within greater than 8 but 26 weeks or less of symptoms. ALF is now the accepted terminology to encompass this entire spectrum of patients.[1] In pediatric patients, ALF is

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defined with slight modification owing to difficulties diagnosing encephalopathy and also owing to frequent occult chronic liver disease.[2]

ALF in the Pediatric Population (Pediatric ALF Study Group Definition)

- Presence of liver-related illness.
- No known history of prior chronic liver disease.
- Coagulopathy not corrected by vitamin K.
  - International Normalized Ratio of 1.5 or greater or a prothrombin time of 15 or greater, plus encephalopathy.
  - International Normalized Ratio of 2.0 or greater or a prothrombin time of 20 or greater, with or without encephalopathy.

The lack of prior liver disease is important in distinguishing ALF from the more recently recognized clinical entity of acute-on-chronic liver failure.[3] The latter, although currently without a consensus definition, is characterized by acute hepatic dysfunction in patients with preexistent chronic liver disease associated with multiorgan failure and high short-term mortality.

ALF classification systems such as O'Grady, Bernuau, and Japanese have defined disease by timing of symptoms as hyperacute, acute, or subacute; fulminant or subfulminant; and fulminant or late onset disease, respectively. Such classifications may help to define the etiology and pathologic presentation, as well as likely complications and prognosis; acetaminophen (paracetamol) and viral injury are prone to hyperacute presentation, whereas idiosyncratic drug-induced liver injury, Wilson's disease, or autoimmune hepatitis may present less acutely.[4–7] Clinical features include hepatic encephalopathy, coagulopathy, systemic inflammatory response syndrome, and multiorgan failure.[4] Death occurs in up to 50% of patients, so pathologists may encounter these types of specimens at biopsy, native liver at transplantation, and also during postmortem examination. The most common causes of death in ALF are sepsis and cerebral edema.[8]

ETIOLOGY

ALF is as varied etiologically as chronic liver disease[1,8] (**Box 1**), and approximately 15% are of unknown cause in adults (higher in children, approximately 50%). In developing countries, hepatotropic viral infection (hepatitis A, E, and/or B) is the most common cause of ALF. Hepatitis A and E are responsible for most cases worldwide.[9]

Hepatitis A

- Single-stranded RNA virus (*picornaviridae*).
- Acute self-limited hepatitis common (especially in children); ALF is rare (<1%); no chronic disease.
- Approximately 31% of patients with hepatitis A-induced ALF require transplantation or expire.
- The pathogenesis of development of ALF are poorly understood.
  - Evidence is inconclusive as to whether a viral sequence specific to ALF cases exists; there is stronger evidence for the role of cytotoxic T-cell response in determining course of disease.
- Serologic studies are available for immunoglobulin (Ig)M and IgG, and polymerase chain reaction (PCR) assays to detect viral RNA.

Hepatitis E

- Small, nonenveloped positive strand RNA virus (*hepeviridae*).
- May be associated with epidemic outbreak; it accounts for 20% to 40% of ALF in developing countries.