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# Asparaginase-Induced Hepatotoxicity

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## Abstract Text

**Background:**

Asparaginase, an anti-neoplastic agent commonly used to treat leukemia, is a bacterial-derived enzyme that catalyzes the hydrolysis of asparagine, an amino acid important for protein production. In the ongoing Drug-induced Liver Injury Network (DILIN) prospective study, asparaginase was the most frequent cause of liver injury with jaundice among anti-cancer agents (8 of 40: 25%). We describe the pattern of hepatotoxicity and unique features of injury from this drug.

**Methods:**

Eight cases from 5 DILIN centers were reviewed including the clinical course, laboratory values, imaging studies, and histopathology.

**Results:**

The cohort consisted of 7 women ages 28 to 59 years and one 8-year old boy, all with acute or chronic lymphocytic leukemia. 7 were Caucasian and 1 African American. 2 patients received asparaginase, 5 pegaspargase and 1 both. The mean time to onset of jaundice was 15 days (range 9 to 21 days), generally during the first course (n=6) or early during the second (n=2). Symptoms included jaundice (n=8), fatigue (6), and abdominal pain (6) but rarely itch (1). Initial mean serum ALT level was 396 U/L (range 83 to 1076), Alk P 195 U/L (64 to 452), and bilirubin 5.0 mg/dL (3.7 to 8.4). Bilirubin levels rose thereafter despite stopping drug to mean peak values reaching 17.6 mg/dL (11.7 to 25.7). Jaundice persisted for up to several months and delayed re-initiation of chemotherapy in all subjects. Peak INR values ranged from 1.1 to 1.7 and nadir of serum albumin from 1.5 to 2.6 g/dL. Tests for hepatitis A, B, C and E were negative in all, and only 2 patients had autoantibodies (ANA 1:80 and 1:160). Hepatic imaging revealed fatty liver in all patients, ascites in 2 and hepatomegaly in 1. Liver biopsy from one patient showed diffuse macrovesicular steatosis, intrahepatic cholestasis and minimal hepatocyte necrosis. One patient who was restarted at the same dose re-developed less severe liver injury (peak bilirubin 3.8 mg/dL). Two patients died within 6 months of onset, but death was attributed to leukemia in both.

**Conclusion:**

Asparaginase is a common cause of antineoplastic induced liver injury, typically with short latency, marked steatosis, and prolonged cholestasis, which can delay cancer treatment. The etiology of injury may be inhibition of essential hepatocyte protein synthesis and function from asparagine deficiency. Therapies restoring amino acid balance may ameliorate the course and allow for more rapid re-initiation of therapy.

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