Drug-induced Liver Injury

The Hepatic Pathologist's Approach

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KEYWORDS

• Hepatotoxicity • Acute liver failure • Acute hepatitis • Hepatic necrosis • Cholestasis

KEY POINTS

- Hepatic pathology in drug-induced liver injury is complex, but may be approached systematically.
- Biopsy assessment begins with objective evaluation of the character and severity of histologic changes.
- The histologic findings are summarized as a pattern of injury that generates the histologic differential diagnosis.
- The pathologist provides an expert interpretation of the findings in light of the patient's medical and drug history.

INTRODUCTION

Evaluation of a liver biopsy in a suspected case of drug-induced liver injury (DILI) can be a daunting experience. Unlike the well-defined and commonly encountered patterns of chronic hepatitis and fatty liver disease, a biopsy in a case of DILI can show a wide variety of histologic findings, including inflammation, necrosis, cholestasis, fibrosis, nodular regeneration, vascular injury, and duct destruction. These histologic lesions can be arranged in combinations that can be difficult to classify into recognizable patterns of liver injury. Nevertheless, the determination that a drug is or is not involved in liver injury has real clinical consequences and a liver biopsy can provide a wealth of information on both the pattern of injury and its severity, guiding both determination of the cause of the injury as well as subsequent clinical decision making.

Because of the inherent complexity of the pathology, the pathologist must approach the biopsy with a systematic evaluation plan. This article outlines one possible method, beginning with objective assessment of the extent and pattern of hepatic

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injury, followed by correlation with the clinical history and laboratory findings and then an assessment of both the likelihood and the specific cause of DILI. Although most of the discussion relates to evaluation of injury related to prescription and nonprescription medications, these same principles apply to the evaluation of injury related to environmental and occupational toxins and injury caused by herbal and dietary supplements. Therefore, although it is not explicitly stated in every instance, the term DILI should also be understood to include these other causes as appropriate.

USE OF THE LIVER BIOPSY IN DRUG-INDUCED LIVER INJURY

A liver biopsy is not required to evaluate a patient with suspected DILI. In the US Drug-Induced Liver Injury Network (DILIN), only 50% of patients enrolled in the prospective protocol underwent liver biopsy during the course of their evaluation.[1] Unlike autoimmune hepatitis, in which the published algorithms incorporate liver biopsy as part of the diagnosis,[2,3] the most widely used clinical algorithm for DILI determination (the RUCAM [Roussel Uclaf Causality Assessment Method])[4] does not have a place for including the findings of liver biopsies. Nevertheless, when a liver biopsy is performed, there are several questions the pathologist may be asked to address: are the patient's liver abnormalities caused by DILI or some other cause of liver disease? If DILI is likely, can the liver biopsy help define which drug is causing the patient's injury? How severe is the injury and does the inflammatory pattern suggest steroid responsiveness by analogy to autoimmune hepatitis? Can it inform clinicians with respect to mechanism of injury or prognosis?

Once the clinical decision to perform a biopsy has been made, it is important that a plan for biopsy evaluation be made before the procedure. A portion of the biopsy may need to be sent for culture or for viral polymerase chain reaction testing. If mitochondrial injury is suspected, a 1-mm to 2-mm segment may be fixed in glutaraldehyde and sent for ultrastructural examination. Saving a piece frozen for cryostat sections is unlikely to be necessary because most specialized tests can be performed on the formalin-fixed tissue. If staining for fat is desired (as in the case of microvesicular steatosis), a formalin-fixed piece can be cut on a cryostat before processing and stained with oil red O or Sudan black. Contacting the pathologist before the biopsy can be helpful to decide how best to triage the specimen.

The more clinical questions that need to be addressed, the more critical it is to have an adequate biopsy to work with, both for the separate specialized testing outlined earlier and for routine histologic assessment. There have not been studies of biopsy adequacy in DILI, but some answers can be inferred from studies of biopsy adequacy in chronic viral hepatitis and fatty liver disease. Most of these studies have focused on the effects of biopsy size on the staging and grading of chronic hepatitis C. Sampling error is increased with shorter biopsies as well as with those taken with a narrow-gauge needle with a significant underestimation of both grade and stage in biopsies less than 1.5 cm in length or with 10 portal areas.[5–7] Studies of biopsy size in fatty liver disease have shown similar findings.[8] It should be remembered that these studies were performed to identify size limitations with respect to specific biopsy features or for making a specific diagnosis (steatohepatitis). In biopsies performed to evaluate a broad clinical differential diagnosis, these biopsy size estimates should be considered as lower estimates. In order to adequately evaluate injury to ducts[9] and veins, 10 to 20 complete portal areas and a similar number of central veins may be necessary. Given the dependence of observing complete structures on the width of the biopsy and the total number of structures on the biopsy length[10,11] it is reasonable to follow the guidance of the American Association for the Study of Liver Diseases