Recent Advances in the Histopathology of Drug-Induced Liver Injury

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KEYWORDS

• Hepatotoxicity • Acute hepatitis • Autoimmune hepatitis • Hepatic necrosis • Cholestasis

Key points

- Liver biopsy provides clinically useful information on differential diagnosis and character of injury in drug-induced liver injury (DILI).
- The pattern of injury on biopsy relates to the etiologic differential diagnosis, including both drug and nondrug causes.
- Recent reports of DILI show several themes, including injury from herbals and dietary supplements and from traditional pharmaceuticals.
- A variety of immunomodulatory agents have been associated with DILI in recent years, most associated with an autoimmune hepatitis-like injury.

ABSTRACT

Drug-induced liver injury (DILI) is constantly changing as new drugs are approved and as new herbals and dietary supplements (HDS) reach the market. The pathologist plays a key role in the evaluation of DILI by classifying and interpreting the histologic findings considering patients' medical history and drug exposure. The liver biopsy findings may suggest alternative explanations of the injury and additional testing that should be performed to exclude non-DILI causes. Recent reports of iatrogenic liver injury are reviewed with attention to immunomodulatory and antineoplastic agents as well as reports of injury associated with HDS use.

OVERVIEW

Drug-induced liver injury (DILI) is one of the more challenging areas in liver pathology. The complexity

Abbreviations

AIH	Autoimmune hepatitis
CTLA-4	Cytotoxic T-lymphocyte antigen-4
CVID	Common variable immunodeficiency
DIAIH	Drug-induced autoimmune hepatitis
DILI	Drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
HDS	Herbal and dietary supplements
LDO	Large duct obstruction
PBC	Primary biliary cholangitis
PFIC	Progressive familial intrahepatic cholestasis
TNF	Tumor necrosis factor
VBDS	Vanishing bile duct syndrome

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of the challenge derives from multiple sources. There are more than 350 separate drugs that have been associated with some risk of liver injury in the publicly available reference Web site LiverTox (livertox.nlm.nih.gov).[1] Each drug may have one or more characteristic clinical presentations and patterns of injury. In well more than half of these drugs, the type of injury (clinical and/or histologic) has only been the subject of case reports or small series, so the worldwide published experience is very limited. Overall, the incidence of DILI is low, with population-based incidence rates that vary from 8.1 per 100,000 over a 3-year period in France[2] to 19.1 per 100,000 over a 2-year period in Iceland.[3] The incidence of DILI due to any individual drug is difficult to estimate but is certainly much lower. Liver biopsies are not performed on all cases of DILI. In the US Drug Induced Liver Injury Network (DILIN), biopsies were performed in only about 50% of cases and were available for central review in only about 33%.[4] In a similar clinical network established across Spain to register cases of DILI, biopsy results were only available in about 25% of cases.[5] Thus, the potential biopsy material available for review to any one pathologist will be limited, even at busy academic medical centers. The challenge is compounded by comorbidities that affect the liver and by polypharmacy. Pathologists, as the expert interpreters of tissue findings, must strive to discern the diagnostic possibilities and to offer alternative, non-DILI possibilities for the injury. This review covers both the basic evaluation of the liver biopsy in cases of suspected DILI as well as some of the recent published information on DILI histology.

EVALUATION OF THE LIVER BIOPSY

Because a liver biopsy is not a required part of the workup for a case of suspected DILI, the clinician submitting the biopsy will likely have questions about the cause of the liver injury. They may be looking for the pathologist to confirm their clinical suspicion of DILI when most of the other possibilities have been excluded or DILI may be only one of several possible etiologic considerations. In some cases, the drug may be providing a clear therapeutic benefit and the clinician may be looking for guidance as to whether the drug may be safely continued, as in the case of methotrexate. Finally, DILI might not be suspected at all but might be suggested by the pathologist.

Fig. 1 diagrams an approach to the liver biopsy in cases of suspected DILI.[6] It is best to start with an unbiased evaluation of the liver pathology to determine a pattern of injury. The liver, like other organs, shows stereotyped responses to injury that can be organized into particular patterns related to differential diagnosis. Hans Popper and colleagues[7] were the first to categorize DILI in this fashion, dividing cases into 6 histologic patterns of injury: zonal necrosis, hepatitis with or without cholestasis, acute hepatitislike with or without massive necrosis, simple cholestasis, reactive hepatitis, and steatosis. The US DILIN used a larger classification of 18 categories in its blinded review of cases of suspected DILI. **Table 1** organizes the patterns of injury into those that have been most commonly observed in studies of acute DILI and those that are less common. In this DILIN study, necro-inflammatory and cholestatic patterns accounted for 86% of the cases,[8] whereas all but one of the cases in Popper and colleagues' study[7] and 95% of the cases in Andrade and colleagues' study[5] could be placed into one of these 7 patterns. The steatotic patterns are relatively rare. Macrovesicular steatosis and steatohepatitis present with modest elevations of aminotransferases and normal bilirubin and so fail to meet the protocol entry requirements,[9] whereas drug-induced microvesicular steatosis is restricted to a limited list of agents that primarily injure mitochondria.[10] The vascular injury patterns are also uncommon in the large cohort studies, which may also relate to case selection bias and a limited number of implicated agents.[11] The patterns of glycogenosis,[12,13] ground-glass cell change,[14] and inclusions[15,16] may sometimes be associated with sufficient laboratory abnormalities to result in a biopsy but are uncommon in the cohort studies.

Once the biopsy has been evaluated for the pattern of injury, and the severity of the lesions has been assessed, the pathologist should establish the non-DILI histologic differential diagnosis (see **Table 1**). This process can be analyzed with respect to the clinical history and laboratory and imaging findings. The emphasis should be placed on identifying a non-DILI explanation for the injury, as DILI should always be a diagnosis of exclusion. Depending on the clinical evaluation before liver biopsy, additional testing may be suggested by the histologic injury pattern. Checklists of information recommended for publication of DILI cases can be used to identify potentially useful tests.[17] If DILI cannot be excluded, the possibility that DILI caused the injury can be entertained. The patients' list of medications can be evaluated for suspects based on several factors, including the temporal exposure to the medication and the likelihood of the medication to cause the pattern of injury observed. Drugs tend to be associated with some injury patterns more than others. For example, minocycline is usually associated with noncholestatic hepatitis patterns, occasionally with cholestatic hepatitis and not associated with zonal necrosis or acute cholestasis.[8,18]