Drug-induced hepatitis: histologic clues to a difficult diagnosis

Feriyl Bhaijee

Robert A Anders

Abstract

Drug-induced liver injury (DILI) results from two chief mechanisms of action: idiosyncratic hepatotoxicity, which typically manifests with prominent inflammation, and intrinsic hepatotoxicity, which demonstrates necrosis with negligible inflammation. Clinically, DILI is classified into hepatitic, cholestatic, or mixed presentations based on the pattern of liver enzyme elevation. As many etiologic factors can result in abnormal liver enzymes, the clinical clue to diagnosing DILI is symptomatic and biochemical improvement upon withdrawal of the offending agent. Histologically, DILI manifests in four main patterns of injury: i) inflammation-predominant acute hepatitis, ii) necrosis-predominant acute hepatitis, iii) resolving hepatitis, and iv) syncytial giant cell hepatitis. In contrast to the characteristic features of both acute hepatitis and syncytial giant cell hepatitis, resolving drug-induced hepatitis lacks specific histologic features and may mimic other mild forms of chronic hepatitis. Ultimately, the presence of sinusoidal PASD + Kupffer cell aggregates − in the absence of significant hepatocellular inflammation or injury − is the histologic hallmark of resolving drug-induced hepatitis.

Keywords DILI; drug injury; drug-induced; hepatitis; Kupffer cell; statin

Case report

A 51-year-old man with a history of obesity, type 2 diabetes mellitus, hypertension, and hypercholesterolemia presented with recent-onset fever, abdominal pain, and nausea. His chronic medications included metoprolol (for the past 5 years) and a statin, which was initiated 6 weeks prior to presentation. A liver function panel prior to initiation of statin therapy was within normal limits, with a serum aspartate aminotransferase (AST) of 18 U/L, alanine aminotransferase (ALT) 25 U/L, alkaline phosphatase (ALP) 60 U/L, and total bilirubin 0.5 mg/dL. He reported no significant alcohol use. Physical examination at presentation revealed right upper quadrant tenderness; jaundice was notably absent. Radiologic studies ruled out hepatic vein thrombosis and biliary dilatation. Serum testing showed the following: AST 53 U/L, ALT 171 U/L, ALP 110 U/L, and total bilirubin 1.2 mg/dL. Serologic testing was negative for viral hepatitides A, B, and C (with hepatitis B surface antibody present secondary to previous vaccination). Serum autoantibodies (anti nuclear, anti mitochondrial, and anti smooth muscle) were likewise negative. As viral, autoimmune, and alcoholic hepatitides were clinically excluded, a presumed diagnosis of drug-induced liver injury (DILI) was rendered and statin therapy was discontinued. The patient received symptomatic therapy for his acute symptoms, which resolved over the following days.

Three weeks later, his liver enzymes had improved but not quite normalized and a liver biopsy was performed in order to evaluate possible etiologic factors for the hepatic injury.

Histologic findings

The needle core biopsy demonstrated mild lobular inflammation, minimal hepatocellular injury, and prominent clusters of sinusoidal Kupffer cells, which were highlighted by periodic acid-Schiff with diastase digestion (PAS-D) (Figures 1 and 2). There was no significant steatosis, bile duct injury, or cholestasis. The overall histologic picture suggested a resolving hepatitis pattern of injury, as is often a result of DILI, but can also be seen in the resolving phase of any acute hepatitis.

Discussion

Drug-induced liver injury (DILI) is defined as liver injury caused by exposure to a drug or non-infectious toxic agent resulting in organ dysfunction, as assessed by clinical and/or biochemical markers. While universally acknowledged as a significant cause of both acute and chronic liver injury, the reported incidence of DILI varies widely and is thought to be underestimated. Like all diagnoses of exclusion, judicious clinical assessment relies on a high index of suspicion in addition to meticulous history-taking and subsequent ancillary testing.

The two chief pharmacological mechanisms of action of DILI include *idiosyncratic hepatotoxicity*, which is more common and typically manifests with prominent inflammation, and *intrinsic hepatotoxicity*, which demonstrates necrosis with negligible inflammation. Regardless of the underlying mechanism, the clinical presentation of DILI is classified based on the pattern of liver enzyme abnormalities: i) *hepatitic* presentations include acute hepatitis − with or without autoimmune markers that may mimic autoimmune hepatitis − and can progress to chronic hepatitis; ii) *cholestatic* injury shows elevation of ALP with minimal transaminitis; and iii) *mixed* presentations include features of both (Table 1).[1,2] Duration of injury differentiates acute from chronic DILI. While almost every type of therapeutic agent has the potential to cause liver injury, the most common offenders belong to a relatively small group of drugs (Table 2).

Establishing drug injury as the cause of liver damage requires both clinical and histologic data. Not only is an exhaustive drug history required, including herbal and over-the-counter agents, but the temporal onset of liver dysfunction is key to making the diagnosis. Liver dysfunction may present weeks to months after initiation of the offending agent and even after it has been discontinued, further obscuring the etiology of hepatotoxicity. Moreover, the presence of serum autoantibodies may render DILI indistinguishable from de novo autoimmune hepatitis. Ultimately, the clinical clue to diagnosis comprises symptomatic and

Feriyl Bhaijee *MD Pathology Fellow, AmeriPath Indiana, Indianapolis, IN, USA. Conflicts of interest: none.*

Robert A Anders *MD PhD Associate Professor of Pathology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none.*

Please cite this article in press as: Bhaijee F, Anders RA, Drug-induced hepatitis: histologic clues to a difficult diagnosis, Diagnostic Histopathology (2017), https://doi.org/10.1016/j.mpdhp.2017.11.003

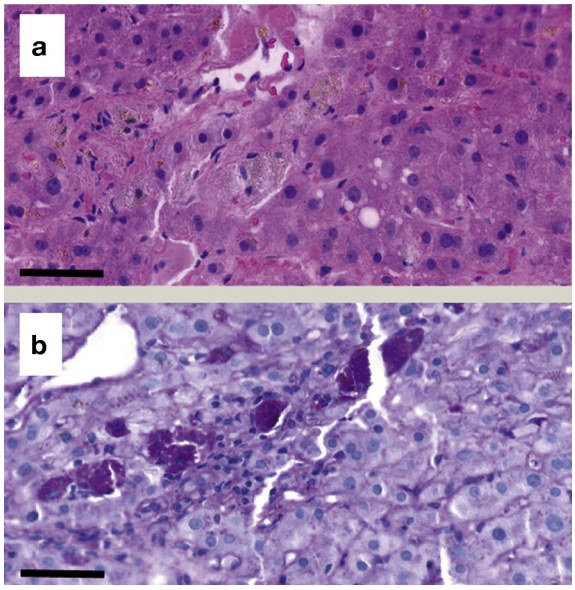

Figure 1 H&E, needle biopsy demonstrating mild lobular inflammation, minimal hepatocellular injury, and prominent clusters of sinusoidal Kupffer cells.

biochemical improvement upon withdrawal of the offending agent.

While most cases resolve following discontinuation of the inciting drug, some cases persist for weeks to months and are more likely to be biopsied. Histologically, DILI results in four main patterns of injury: i) inflammation-predominant acute hepatitis, ii) necrosis-predominant acute hepatitis, iii) resolving hepatitis, and iv) syncytial giant cell hepatitis (Table 3, Figure 2). *Inflammation-predominant acute hepatitis*, as the name suggests, comprises both portal and lobular lymphocytic inflammation, with variable necrosis, and regenerative features such as binucleated hepatocytes and thickened cell plates. Sinusoidal Kupffer cells may be prominent and fibrosis is notably absent. Various other nonspecific histologic findings, such as bile duct injury, eosinophilia, granulomas, and cholestasis out of proportion to hepatocellular injury ("bland lobular cholestasis,") are also frequently seen in this pattern of injury. While

CIOMS consensus criteria for terminology in DILI[1,2]

Terminology	Criteria
Hepatocellular injury	Isolated increase in ALT >2× normal, or ALT/ALP ratio >5
Cholestatic injury	Isolated increase in ALP >2× normal, or ALT/ALP ratio <2
Mixed injury	Both ALT and ALP increased; ALT/ALP ratio 2–5
Acute injury	Above changes present <3 months
Chronic injury	Above changes present >3 months
Chronic liver disease	This term is used only after histologic confirmation

Table 1

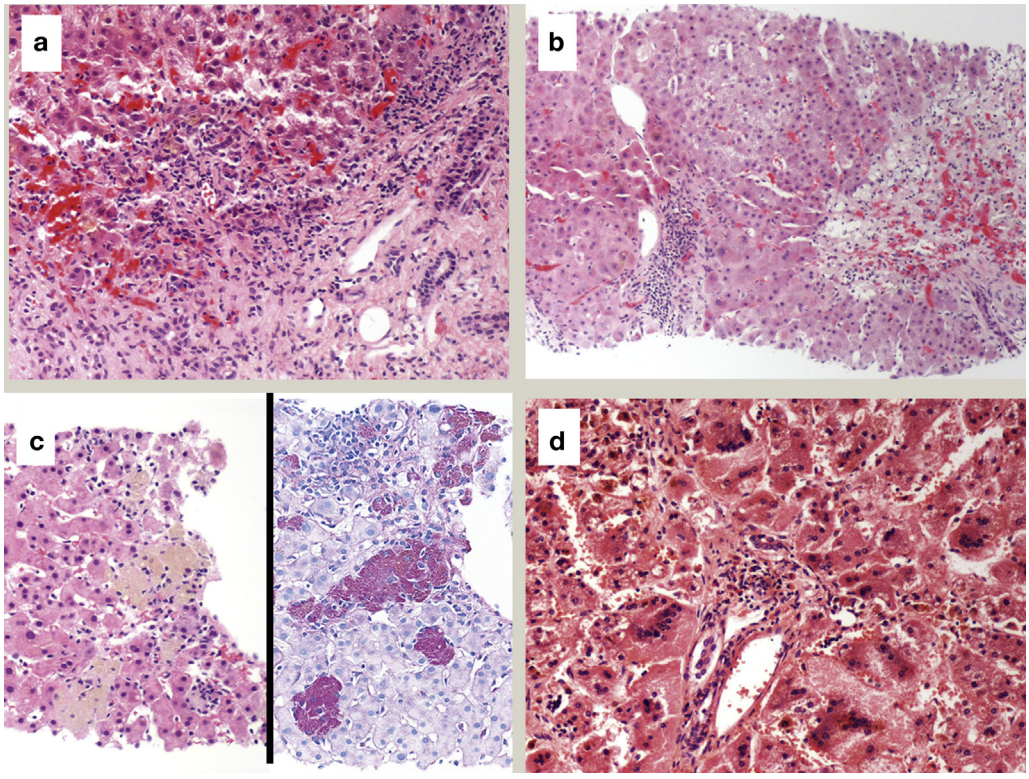

Figure 2 Periodic acid-Schiff with diastase digestion (PAS-D) stain, highlighting clusters of sinusoidal Kupffer cells.

Please cite this article in press as: Bhaijee F, Anders RA, Drug-induced hepatitis: histologic clues to a difficult diagnosis, Diagnostic Histopathology (2017), https://doi.org/10.1016/j.mpdhp.2017.11.003