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DRUG-INDUCED LIVER INJURY (P HAYASHI, SECTION EDITOR)

Bile Duct Injury Due to Drug-Induced Liver Injury

Priya Grewal[1] · Jawad Ahmad[1]

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Abstract

Purpose of Review Drug-induced liver injury (DILI) can present with a variable clinical and pathological phenotype and can be classified using liver enzymes as hepatocellular, cholestatic, or a mixed pattern. The cholestatic pattern has been considered amongst the spectrum of direct liver damage at the microscopic level, but recently, bile duct injury, as a manifestation of DILI, has emerged as a distinct entity, and this review examines several examples of biliary tract abnormalities due to DILI from a clinical, radiologic, and pathologic perspective.

Recent Findings Case series and reports have emerged over the last few years of drugs causing cholangiographic changes or direct injury to the intra- and extra-hepatic biliary tree, such as ketamine and several chemotherapy agents. The DILI Network (DILIN) in the USA has published their experience of cases with vanishing bile duct syndrome on histology and sclerosing cholangitis-like changes seen on cholangiography. The pathogenesis of these changes is unclear but it appears that this type of injury is more severe and more likely to lead to a chronic injury with increased mortality than other cases of DILI.

Summary Bile duct injury due to DILI is an increasingly recognized entity and imaging of the biliary tree in conjunction with liver biopsy should be considered in patients with severe cholestatic DILI.

Keywords Drug-induced liver injury (DILI) · Cholangitis

Abbreviations

ALT	Alanine aminotransferase
Alk P	Alkaline phosphatase
AST	Aspartate aminotransferase
DILI	Drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
MRCP	Magnetic resonance cholangiopancreatography
SC	Sclerosing cholangitis
VBDS	Vanishing bile duct syndrome

Introduction

Idiosyncratic drug-induced liver injury (DILI) has a variable clinical, biochemical, and histopathologic presentation that can mimic nearly all known forms of liver disease [1–3]. DILI can be classified by the type of liver injury into hepatocellular, cholestatic, and mixed depending on the R ratio ([alanine aminotransferase/upper limit of normal] ÷ [alkaline phosphatase/upper limit of normal]). Hepatocellular cases are defined on the basis of $R > 5$, cholestatic if $R < 2$ and mixed if $R = 2–5$. Cholestatic liver injury accounts for 20–40% of all DILI cases and the clinical spectrum includes bland cholestasis, cholestatic hepatitis, vanishing bile duct syndrome (VBDS), and secondary sclerosing cholangitis (SSC). While cholestatic hepatitis is the most common form of DILI leading to cholestasis, there are emerging reports that DILI can directly lead to bile duct injury such as VBDS [4••] and sclerosing cholangitis-like (SC-like) changes of the biliary tree [5, 6••]. The mortality of cholestatic DILI can be as high as 12%, and thus, prompt recognition and removal of the implicated agent(s) are of paramount importance [7].

This article is part of the Topical Collection on *Drug Induced Liver Injury*

✉ Jawad Ahmad
jawad.ahmad@mountsinai.org

[1] Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Chemotherapy-Related Changes to the Biliary Tree

Initial reports of DILI leading to sclerosing cholangitis implicated chemotherapeutic agents, specifically fluoropyrimidines, floxuridine, and 5-fluorouracil, infused through the hepatic artery for the treatment of hepatic metastasis from colorectal cancer [8, 9]. The biliary tree derives its

vascular supply almost exclusively from branches of the hepatic artery and so is sensitive to any interruption of this supply. Chemotherapy-induced cholangitis results from effects of chemotherapy on the microvascular circulation of biliary endothelial cells leading to ischemia and less so from the intra-arterial catheter manipulation. Additionally, cases have been reported of systemic chemotherapy with docetaxel for metastatic prostate cancer causing an SC-like picture after 2 months of treatment [10]. Docetaxel undergoes extensive hepatic metabolism, biliary excretion, and fecal elimination. Concomitant use of drugs that inhibit the metabolism and elimination of docetaxel, such as carvedilol, bicalutamide, and dronedarone, lead to a marked increase in hepatic accumulation of the drug and bile duct injury. This injury is speculated to result from dose-dependent intrinsic vascular toxicity of the drug with a minor immune component.

Ketamine Cholangiopathy

Recurrent and prolonged recreational use of inhaled ketamine for its hallucinogenic and euphoric properties is common in Asia, especially in Taiwan and Hong Kong and rising in the UK. Ketamine has been linked with biliary tract changes particularly diffuse large duct dilation after several years of use [11]. A recent study demonstrated distinctive cholangiographic changes in a large cohort of recreational ketamine users [12•]. More than 60% of 343 patients had either diffuse extrahepatic dilation, fusiform extrahepatic dilation, or intrahepatic ductal changes. These changes were predicted by an elevated Alk P level and were reversible after abstinence in most cases. Ketamine can also cause intrahepatic ductal strictures with an SC-like picture but interestingly, jaundice is rare [13, 14].

US Drug-Induced Liver Injury Network Experience

The pathogenesis of cholestatic or mixed type liver injury may result from immunologically mediated injury to the biliary tree. In patients with DILI who develop an acute cholestatic injury, particularly if severe, prolonged cholestasis can occur and two patterns of liver injury may emerge. The first pattern is that of bile duct loss leading to VBDS with characteristic changes on liver biopsy [4••], while the second pattern is that of a secondary SC-like picture apparent on biliary imaging such as magnetic resonance cholangiopancreatography (MRCP) [5, 6••]. On reviewing the literature, it is unclear whether these two patterns of liver injury are unique phenotypes of cholestatic liver injury or whether they can co-exist or progress from one to the other.

Vanishing Bile Duct Syndrome

A third of patients enrolled in the prospective US Drug-Induced Liver Injury Network (DILIN) study underwent liver biopsies and on review, 26 of 363 cases (7%) cases of DILI had histological evidence of bile duct loss [4••]. These patients typically had a moderate-to-severe acute cholestatic liver injury with immuno-allergic features, with nearly 40% of the patients developing a rash and some progressing to a severe cutaneous reaction such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Of concern, a histological finding of bile duct loss was associated with progression to chronic liver injury (defined as lasting longer than 6 months) in more than 90% cases and carried a 26% mortality. The most common incriminating medications were amoxicillin-clavulanate, herbal and dietary supplements (HDS), azithromycin, fluoroquinolones, and a newer chemotherapeutic agent, temozolomide, used in the treatment of malignant brain tumors. The median latency period for the injury after drug use was 1 month but the range extended to several years. While changes suggestive of SC-like changes were seen in a few ducts in 4 of the 26 biopsies, the paper did not report on any MRCP findings in these patients. Since tertiary referral centers were enrolling patients in the DILIN, the study likely enrolled more severe chronic cases, accounting for the higher incidence of VBDS and poorer outcomes for the group as a whole and especially so in the African-American patients. A bile duct loss greater than 50% predicted a poor outcome. Table 1 illustrates some of the clinical characteristics of DILIN patients with VBDS compared to those without VBDS on biopsy. VBDS patients had more cholestatic injuries and significantly worse outcomes with a 3-fold increase in all-cause mortality.

Sclerosing Cholangitis-Like Changes

A recent study from the DILIN prospective cohort identified 4 cases of drug-induced SC-like changes (7%) from a total of 56 patients who had undergone biliary imaging by MRCP during the workup of jaundice to rule out concomitant biliary pathology in patients with DILI [6••]. The study reviewed DILI patients who underwent MRI abdomen and had adequate MRCP imaging that were centrally read by 2 experienced experts in biliary radiology. The authors suggest that the 7% incidence was an underestimation because reports of MRCP images not available for review and therefore not included in the study suggested cholangiographic changes in other patients with cholestatic DILI. A representative MRCP from one of the 4 patients is shown in Fig. 1 with evidence of discrete intra-hepatic biliary strictures and dilation. Table 2 shows some of the clinical characteristics of these 4 patients with SC-like changes on MRCP. The medications implicated were moxifloxacin, atorvastatin, and 2 different HDS. Three patients developed chronic DILI and 1 patient required liver transplantation. One of the cases was hepatocellular rather than cholestatic and this patient underwent repeat MRCP 18 months after the initial injury demonstrating resolution of the cholangiographic findings.

Table 1 Clinical and laboratory features of 26 patients with VBDS compared to non-VBDS patients with liver biopsies in the DILIN prospective cohort (taken from reference 4)

	VBDS ($N = 26$)	No VBDS ($N = 337$)	P value
Median age (years)	53	50	NS
Sex (% female)	54%	60%	NS
Median peak ALT (U/L)	497	713	0.17
Median peak AlkP (U/L)	804	297	< 0.001
Median peak bilirubin (mg/dL)	21.5	13.9	< 0.01
Jaundice	96%	78%	0.02
Chronicity at 6 months	94%	47%	< 0.001
Death, all causes	27%	9%	0.01

In an earlier report from Iceland, 25% of DILI patients underwent an MRCP and 40% of these had cholangiographic findings suggestive of SC-like changes [5]. All the patients were female, and the medications implicated included amoxicillin-clavulanate, sevoflurane, amiodarone, infliximab, and green tea extract. Liver biopsies were performed in 4 patients, showing portal inflammation, acute and chronic hepatitis, and canalicular cholestasis, but there was no mention of bile duct loss. Overall, this group fared worse than patients with a pure cholestatic/mixed pattern of injury without SC-like changes. They were more likely to be hospitalized and resolution of their liver injury took several months. The short-term prognosis was good with normalization of liver tests in nearly all the patients, though the biliary strictures persisted in the patient who underwent a repeat MRCP. There was no mention of skin reactions in either of these two cohorts.

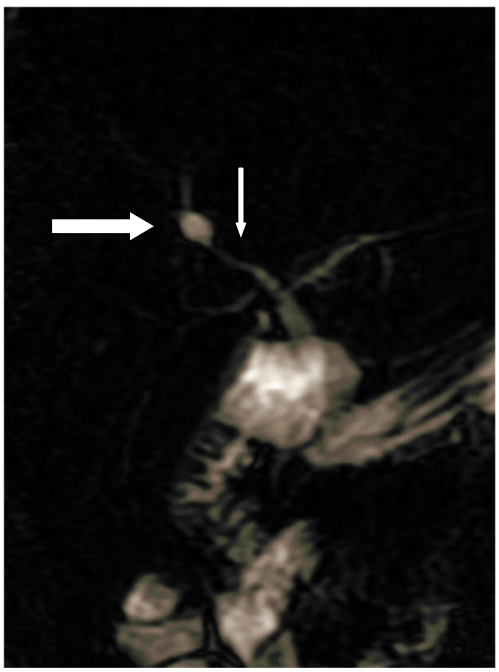

Fig. 1 Coronal MRCP image demonstrating the biliary tree with a focal stricture (small arrow) in the right anterior bile duct with pre-stenotic dilation (larger arrow) (figure Dr. Jawad Ahmad's personal collection)

Pathogenesis of Bile Duct Damage

The pathogenesis of damage to the biliary tree in DILI is unclear. Biotransformation of drugs in the liver occurs in phase I and phase II reactions. The most common phase I drug metabolizing enzymes are represented by the CYP450 superfamily. During phase II drug metabolism, the metabolites from phase I pathways are enzymatically conjugated with hydrophilic endogenous compounds such as glutathione. The detoxification capacity of the liver has been mainly attributed to hepatocytes although the drugs are excreted into the bile, exposing the cholangiocytes to high concentrations of potentially reactive species. Cholangiocytes isolated from rat livers lack CYP 450 and have a low concentration of protective glutathione making them particularly susceptible to drug-induced injury [15]. Conjugation activity has been detected in primary cholangiocytes isolated from humans [16]. The transcripts and proteins include CYP1A, CYP2E1, and CYP3A. Interestingly, while CYP2E1 exhibited a similar pattern of expression in small and large cholangiocytes, CYP3A was detected only in medium and large intrahepatic ducts. This may explain the differential pattern of bile duct injury seen in VBDS and sclerosing cholangitis. In addition, the chemical and structural features of the drug, the genotypic variations of the patient, and other epigenetic aspects are likely to contribute to the development of DILI affecting different segments of the biliary tree.

In DILI affecting the biliary tree leading to SC-like changes, the inciting injury to the biliary epithelium may be an immune-mediated hypersensitivity reaction or perhaps a drug-induced toxic vasculitis given the sensitivity of cholangiocytes to ischemia. In severe cases of cholestatic liver injury, the SC-like changes may result from a collapse of liver parenchyma leading to architectural disarray and distortion of the biliary tree. While there is considerable overlap in the incriminating drugs leading to VBDS and SC, the patients with VBDS have a poorer outcome, more chronicity, and less reversibility. In both the Icelandic and DILIN cohorts of SC-like changes, the majority of patients eventually improved but very few had serial MRCPs images to review. The lack of MRCPs performed in the overall DILIN cohort, particularly the patients who developed VBDS, leaves open the question

Table 2 Characteristics of 4 patients with sclerosing cholangitis-like changes and DILI enrolled in DILIN (data taken from reference 6)

Patient	Age/ years/ sex	Peak bilirubin/mg/ dL	Peak ALT/U/L	Peak Alk P/U/L	Implicated drug	Injury pattern	Chronic injury
1	47/F	15.3	395	603	Moxifloxacin	Cholestatic	Yes
2	77/M	30.1	2506	245	Atorvastatin	Hepatocellular	Yes
3	50/F	17.8	630	982	HDS	Cholestatic	Yes
4	50/M	11.8	397	461	HDS	Cholestatic	No

of whether more patients with cholestatic DILI may demonstrate a "cholangiopathy" that improves as the injury improves, or perhaps evolves into attenuation of the entire biliary tree, correlating with worsening of strictures on MRCP.

The cholangiocyte lines the entire biliary tree originating as the biliary lining of the canal of Herring, all the way to the larger intrahepatic ducts and finally the extrahepatic biliary tree. VBDS targets the small bile duct group with a bile duct diameter of 30 μm or less. This group includes ductules, interlobular ducts, and septal ducts which can easily be missed in a liver biopsy with an insufficient number of portal tracts. Septal ducts drain into area ducts. Sclerosing cholangitis affects mainly the large intrahepatic bile ducts including area ducts, segmental ducts, the right and left hepatic ducts, and sometimes the extrahepatic biliary tree. The differential expression of the conjugating enzymes in the small and large cholangiocytes lining the biliary tree may partially explain the unique pattern of liver injury that evolves as a result of exposure to different drug classes.

Management

The management of bile duct injury due to drugs is primarily contingent upon early recognition and prompt withdrawal of the offending agent. Care should be taken to avoid inadvertent re-challenge. Symptom control is the mainstay of treatment. Ursodeoxycholic acid (UDCA) may be used in cholestatic DILI [17] as it is in many other cholestatic diseases given its protection against cytotoxicity caused by toxic bile salts, stimulation of hepatobiliary secretion, antioxidant activity, enhancement in glutathione levels, and inhibition of liver cell apoptosis and promotion of hepatocyte survival through activation of the epidermal growth factor receptor. A case report outlined improvement in drug-induced bile duct injury using long-term immunosuppression with low-dose mycophenolate mofetil [18]. Anecdotal success in the treatment of drug-induced cholangiopathies unresponsive to UDCA alone was reported using plasmapheresis and methylprednisolone [19].

Management of pruritus secondary to severe cholestasis includes the use of cholestyramine, antihistamines, rifampin, phenobarbital, and opioid analogues. Ultraviolet B phototherapy and plasmapheresis are alternative treatments in those who have failed medical therapy.

ERCP for management of biliary strictures could be considered, but usually, the SC-like changes in the biliary tree resolve as the liver tests improve with discontinuation of the drug.

Conclusion

The diagnosis of DILI relies on exclusion of other causes of liver disease such as viral, autoimmune, and metabolic disease. In addition, liver and biliary imaging is usually required to exclude the possibility of biliary tract disease or choledocholithiasis, particularly in cholestatic DILI. This review highlights that changes in the biliary tree visible on MRCP can occur in DILI, with specific examples such as chemotherapy drugs and ketamine, but even with a wide variety of other agents that can typically cause the whole spectrum of DILI such as amoxicillin-clavulanate or HDS. Previous single-center case reports suggesting the entity of SC-like changes as a manifestation of DILI have now been reinforced by larger multicenter DILI networks both in Iceland and the US confirming that up to 10% of DILI cases who underwent MRCP had images suggestive of sclerosing cholangitis [5, 6••].

The use of MRI in patients with acute and chronic liver disease has evolved over the last decade as concerns increased over the radiation associated with CT scan and the lack of sensitivity of ultrasound to detect subtle changes in the biliary tree. In hospitalized patients with acute liver injury and jaundice, many physicians obtain an MRCP to better define pancreaticobiliary anatomy and in decision making regarding a potential endoscopic or radiologic intervention. Recent guidelines from the American College of Gastroenterology suggest obtaining an MRI/MRCP in patients with cholestatic liver injury (with or without jaundice) [20] and the American College of Radiology appropriateness criteria suggest that MRI/MRCP is an appropriate imaging test in patients with jaundice (with or without symptoms) [21]. In the DILIN prospective study, MRCP was not a common part of the initial work up in suspected DILI having been performed in only 16% of enrolled patients. Hence, SC-like changes may be more common than currently reported. An important caveat is to exclude the possibility of primary sclerosing cholangitis (PSC) as the cause of the biliary tree abnormalities. In the DILIN, cohort 2 of the patients had normal liver enzymes

documented prior to the liver injury, and in the Icelandic cohort, all the patients recovered. However, PSC has to be considered in the differential of patients with cholestatic liver tests, particularly young patients with inflammatory bowel disease, which furthers the importance of obtaining an MRCP.

A liver biopsy is strongly encouraged in patients with prolonged cholestatic injury to aid in the diagnosis VBDS which carries important prognostic implications. Bile duct loss in greater than 50% portal tracts portends a poor prognosis. The pattern of injury shares common histopathological features with primary biliary cholangitis (PBC) and PSC, with inflammation and necrosis at the level of cholangiocytes. If the injury persists, further bile duct loss and biliary cirrhosis are inevitable. While VBDS is more likely to progress to chronic liver injury, SC-like changes are usually reversible based on existing literature. Additionally, long-standing or remote DILI should be considered in the differential diagnosis of patients presenting with biliary cirrhosis or sclerosing cholangitis lacking clinical and laboratory parameters supporting PBC or PSC.

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Compliance with Ethical Standards

Conflict of Interest Priya Grewal and Jawad Ahmad each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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