

NSAID-associated drug-induced liver injury prior to and following liver transplantation

✉ Mesut Gumussoy¹, ✉ Hale Gokcan¹, ✉ Emin Bodakci¹, ✉ Saba Kiremitci², ✉ Berna Savas², ✉ Ramazan Idilman¹

¹Department of Gastroenterology, Ankara University School of Medicine, Ankara, Türkiye; ²Department of Pathology, Ankara University School of Medicine, Ankara, Türkiye

Dear Editor,

Many drugs have the potential to cause drug-induced liver injury (DILI). Drugs can induce any type of acute and chronic liver damage. However, most DILI cases are idiosyncratic. The presentation, pattern of liver injury, latency, and natural outcome differ widely between drugs and sometimes even with the same drug. Here, we describe a patient with nonsteroidal anti-inflammatory DILI before and after liver transplantation.

Drug-induced liver injury (DILI) is an uncommon but important cause of liver disease. Antimicrobials and nonsteroidal anti-inflammatory drugs (NSAIDs) are leading causes of DILI worldwide.^[1,2] The prevalence of DILI varies geographically due to differing genetic risk factors and environmental factors. In Iceland, the annual incidence rate of DILI was 19.1 cases per 100 000 patients; 43 and 11 per 100 000 for amoxicillin-clavulanate and diclofenac, respectively.^[3] Diclofenac and ibuprofen are the most common responsible agents, accounting for up to 6–7 cases in Iceland and Spain.^[3,4] Most NSAID-induced DILI are asymptomatic or produce mild nonspecific symptoms such as nausea, fatigue, and jaundice, which resolve after withdrawal of the suspected drug. Occasionally, it may progress to severe hepatitis, acute liver failure, or chronic hepatitis.^[5] Most DILI cases are idiosyncratic. The majority of idiosyncratic DILI reactions occur within 5–90 days after initiating the drug.^[6] This latency period varies widely among different drugs and patients. DILI is generally diagnosed by increases in liver injury and cholestatic tests. A careful evaluation of other causes of liver disease should be performed. Liver biopsy is not routinely performed in clinical practice for diagnosis. Here, we describe a case with NSAID-induced DILI before and after liver transplantation.

Case Report

A 43-year-old male patient was admitted to the outpatient clinic for nausea, jaundice, and dark-colored urine in July 2019. He has been taking dexketoprofen/diclofenac sodium twice a week for headaches. He consumed 25 packs of cigarettes per year and 60–70 g of alcohol per week for 2 years. On his physical examination, he was icteric and had mild epigastric tenderness. At that time, his serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 897 U/L (0–50) and 1799 U/L (0–50), respectively. His serum alkaline phosphatase (ALP) level was 141 U/L (40–130), gamma-glutamyl transferase (GGT) 158 U/L (10–71), total bilirubin 7.4 mg/dL (0.1–1.2), direct bilirubin 4.3 mg/dL, and albumin 2.7 g/dL (3.5–5.2). INR was 1.32. Serological studies for viral hepatitis, autoimmune panel, and metabolic panel were all normal. We diagnosed NSAID-induced toxic hepatitis. After the drug was discontinued, his laboratory values returned to the normal range. He was discharged with normal liver tests.

The patient was admitted to our clinic with jaundice 45 days after he was discharged. He was on intermittent NSAIDs. His serum AST and ALT levels were 1391 U/L and 1680 U/L, respectively. His serum ALP level was 113 U/L, GGT 104 U/L, total bilirubin 18.2 mg/dL, and direct bilirubin 14.2 mg/dL. His INR was 3.1. Medical supportive treatment was initiated. Hepatic encephalopathy was developed on the seventh day of hospitalization, and INR was 5.0. Plasmapheresis was started. His clinical status and encephalopathy worsened. Living donor liver transplantation was performed on the 16th day of admission. Explant liver pathology was revealed with submassive necrosis characterized by severe liver parenchyma loss accompanied by a marked ductular reaction and regenerative nodule (Fig. 1a, b). He was discharged from the hospital in Oct 2019.

During the posttransplant follow-up period, liver test abnormality was detected. His serum AST, ALT, ALP, and GGT levels were 407 U/L, 729 U/L, 250 U/L, and GGT 280 U/L, respectively. His total bilirubin level was 2.1 mg/dL. He was on flurbiprofen 2–3 times a month for headaches. Liver biopsy was performed. Liver biopsy revealed mild portal and lobular inflammatory lesion combined with a cholestatic reaction. Remarkable biopsy findings were primarily compatible with drug-induced injury (Fig. 2).

Methylprednisolone was started with a dose of 1 mg/kg per day. His aminotransferase levels were decreased, but cholestatic parameters were stable. Magnetic resonance cholangiopancreatography revealed biliary stenosis on the anastomotic site. A plastic biliary stent was placed during endoscopic retrograde cholangiopancreatography. The patient is currently very well with normal liver tests.

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Corresponding author: Ramazan Idilman; Ankara Universitesi Tıp Fakultesi, Gastroenteroloji Anabilim Dalı, Ankara, Türkiye

Phone: +90 312 363 62 13; **e-mail:** idilman@medicine.ankara.edu.tr



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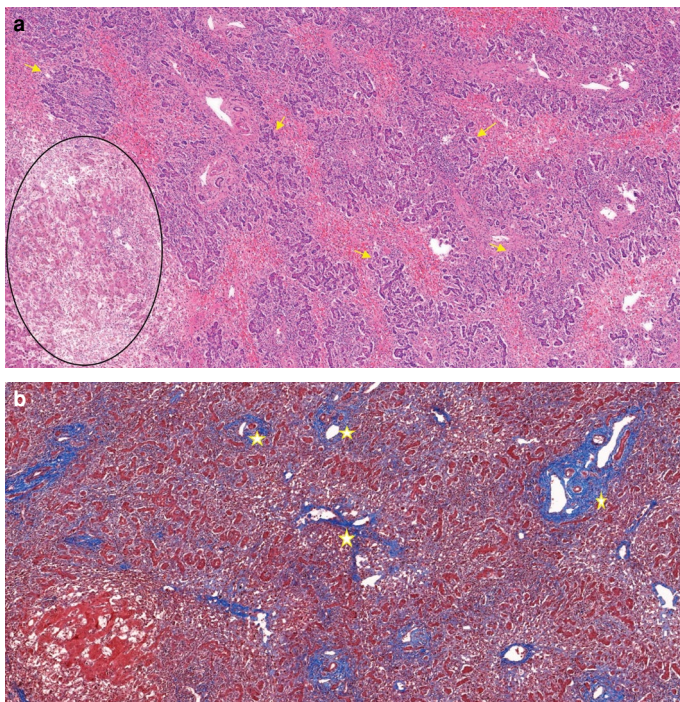


Figure 1. (a) A widespread hepatocyte loss is seen, and the parenchyma is collapsed. Most of the liver parenchyma disappeared due to massive necrosis. Widespread periportal bile ductular reaction (yellow arrows) is prominent, and foci of regenerative nodules are seen (a regenerative nodule area is marked by a circle). **(b)** Trichrome stain highlights the collapsed parenchymal areas, showing prominent ductular reaction and very early fibrosis (light blue) between native portal tracts.

Discussion

Diclofenac is a widely used NSAID and is associated with a high risk of DILI. Many drugs cause idiosyncratic DILI, which is rarely seen and causes unpredictable toxicity.^[7] Idiosyncratic DILI is a multifactorial process and is associated with host-related factors, environmental conditions, and suspected drug properties.^[8,9] The effect of underlying hepatic conditions on DILI is still unclear. A few investigators reported that preexisting liver disease increases the risk of DILI development and increases the risk of a more severe disease outcome.^[9] The pattern of liver injury should be categorized as hepatocellular, cholestatic, or mixed based on the degree/ratio of liver test abnormalities.^[8] The hepatocellular pattern is the most frequent type of liver injury and more commonly leads to a worse outcome compared with other types. Clinical and laboratory features at DILI onset have been associated with the severity and outcome of the disease.^[10] The main therapeutic approach in DILI management is the withdrawal of the offending drug. Clinical improvement is observed after cessation of the drug in most patients. However, idiosyncratic DILI is responsible for around 15% of DILI-induced ALF cases.^[8,10]

In conclusion, DILI remains to be the most common cause of liver test abnormalities. An early and reliable diagnosis is essential.

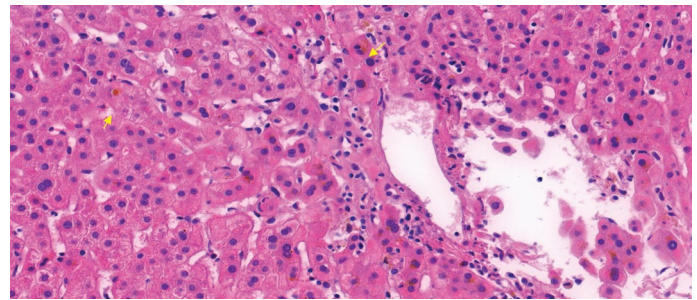


Figure 2. Canalicular cholestasis (yellow areas) is prominent in perivenular areas as evidence of acute cholestasis.

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