Drug Idiosyncrasy Due To Pirfenidone Presenting as Acute Liver Failure: Case Report and Mini-Review of the Literature

Nipun Verma, Pramod Kumar, Suvradeep Mitra, Sunil Taneja, Sahajal Dhooria, Ashim Das, Ajay Duseja, Radha Krishan Dhiman, and Yogesh Chawla

Idiosyncratic drug-induced liver injury (DILI) is ranked among the top most common etiologies of acute liver failure (ALF). It carries poor transplant-free survival. Pirfenidone is an anti-inflammatory and antifibrotic drug that is commonly used for the treatment of idiopathic pulmonary fibrosis (IPF). Hepatotoxicity due to pirfenidone is rare and generally manifests as a mild rise in serum aminotransferases. In this mini-review, we report an unusual case of idiosyncratic DILI due to pirfenidone presenting as ALF, with emphasis on the definition, classification, diagnostic criteria, histopathology, molecular markers, and treatment options for DILI and related ALF. A 77-year-old man with known Parkinson’s disease and IPF presented with jaundice for 7 days and altered mental status for 4 days. His long-term medications included a levodopa/carbidopa combination with a recent addition of pirfenidone over the previous 1 month; there was no monitoring of liver function tests. The evaluation suggested features of acute liver failure with grade III hepatic encephalopathy, acute kidney injury, and metabolic acidosis. The diagnostic workup ruled out viral, toxic, ischemic, and other etiologies for acute liver failure. Based on a Roussel Uclaf Causality Assessment Method score of 7 and possible DILI-ALF, pirfenidone was withdrawn. He was evaluated for liver transplantation but was declined. Despite all supportive measures in intensive care, organ failure progressed and he succumbed to the illness on day 4. Postmortem liver biopsy revealed findings consistent with DILI (final Roussel Uclaf Causality Assessment score, 10). Conclusion: DILI-ALF carries poor prognosis, and liver transplantation should be considered early in the course. Characterization, reporting, monitoring, and labeling of pirfenidone-related hepatotoxicity is vital given its common use in IPF. (Hepatology Communications 2018;2:142-147)

Introduction

Drug-induced liver injury (DILI) is the second most common cause of acute liver failure (ALF). Idiosyncratic DILI accounts for 13%-17% of these cases, and antimicrobials and non-steroidal anti-inflammatory drugs constitute the dominant etiologies. DILI-ALF carries a high mortality with a poor transplant-free survival (27.1%). Pirfenidone is an anti-inflammatory and antifibrotic drug used for the treatment of idiopathic pulmonary fibrosis (IPF). It has been shown to reduce liver fibrosis. Hepatotoxicity with its use is rare and manifests as a mild rise in aminotransferases. We...
report the first case of ALF due to pirfenidone with a mini-review of the literature on DILI and related ALF.

Case Report

A 77-year-old man with no prior liver disease presented to the emergency unit with anorexia and nausea for 2 weeks, jaundice for 1 week, and altered sensorium for 4 days. There was no abdominal pain, distension, constipation, obstipation, or fever. He denied alcohol, herbal or alternative medicine intake, and risk factors for viral hepatitis. Past liver functions and ultrasound of the hepatobiliary system were normal. He had been diagnosed with idiopathic Parkinson’s disease 5 years previously and was on levodopa/carbidopa (300/75 mg/day) with a stable disease. He was recently diagnosed with IPF during an evaluation for dyspnea and had been taking pirfenidone 200 mg 3 times/day for 1 month without any monitoring of liver function tests. Examination revealed tachypnea (rate 35/minute) with low mean arterial pressure (55 mm Hg), malnourishment, icterus, grade III hepatic encephalopathy, and fine crepitations. Investigations showed deranged liver function tests (bilirubin total/conjugated, 12.8/7.5 mg/dL), elevated aminotransferases (aspartate aminotransferase/alanine aminotransferase [ALT], 1260/526 U/L), alkaline phosphatase (ALP, 434 U/L), international normalized ratio (2.1), ammonia (330 l mol/L), and lactate dehydrogenase (689 at admission and 1128 U/L preterminally). He also had acute kidney injury (creatinine, 2.1 mg/dL), lactic acidosis (pH 7.04; HCO₃, 8.2 mmol/L; lactate, 6.1 mmol/L), and recurrent hypoglycemia. An abdominal ultrasound showed a hypoechochogenic liver with reduced span (10 cm) with no evidence of chronic liver disease or biliary dilation. Computed tomography of the head showed cerebral edema (effacement of gyri and sulci with chinking of ventricles). Etiological workup for ALF, including hepatitis B surface antigen; immunoglobulin M hepatitis B core antibody; anti-hepatitis C virus antibody; serologies for hepatitis A, hepatitis E, cytomegalovirus, Epstein Barr virus, and herpes simplex virus; and autoantibodies (anti-nuclear, anti-mitochondrial, anti-smooth muscle, and anti-liver kidney muscle), were all negative. Serum immunoglobulins and ceruloplasmin were also normal. Due to poor prognosis (model for end-stage liver disease score 31; King’s College criteria), the family was counseled for liver transplantation (LT), which was declined. The patient was conservatively managed in the liver intensive care unit with intubation and mechanical ventilation, antihypertensive coma, anti-edema measures, N-acetyl cysteine infusion, 25% dextrose infusion, broad-spectrum antibiotics, hemodialysis for acute renal failure, and supportive care. However, the sensorium progressively worsened to grade IV encephalopathy, and he succumbed on the fourth day of illness due to raised intracranial tension and multiple organ dysfunctions.

Due to the absence of other etiologies, temporal correlation and a Roussel Uclaf Causality Assessment Method (RUCAM) score of 7, we considered the diagnosis of pirfenidone-induced DILI-ALF. The postmortem liver biopsy (Fig. 1) revealed centrilobular confluent hepatic necrosis, bridging necrosis, accumulation of Kupffer cells, and macrophages containing lipofuscin and few surviving swollen and multivacuolated hepatocytes. Most portal tracts showed minimal to mild inflammatory infiltrate containing lymphocytes admixed with a few eosinophils suggestive of drug-induced liver disease (final-RUCAM score, 10; Table 1).

Discussion

DILI is defined as an increase in ALT ≥5 times the upper limit of normal (ULN) or ALP ≥2 times ULN or ALT ≥3 times ULN with bilirubin ≥2 times ULN following drug exposure.⁶ Hy’s law⁷ and the drug-
induced liver toxicity ALF score\(^{(7)}\) predict the development of ALF in DILI. In our case, a >10-fold rise in ALT with jaundice and encephalopathy after drug exposure was consistent with DILI progressing to ALF.

DILI has been classified based on \(R\) values\(^{(8)}\), where \(R\) is defined as serum ALT/ULN divided by serum ALP/ULN. It is labeled as hepatocellular (HC; \(R > 5\)), cholestatic (CS; \(R < 2\)), or cholestatic–hepatitic/mixed (\(R = 2-5\))\(^{(8)}\). Our case had type HC (\(R = 9.6\)). Further, the severity of DILI has been graded on a scale of 0 to 5 based on the presence of jaundice, hospitalization, signs of liver cell failure, organ dysfunctions, and death or LT\(^{(9)}\). Our case had acute liver failure consistent with fatal DILI. Severe or fatal DILI is rare but may constitute up to 15% of ALF cases\(^{(3,5)}\). Also, it is the most common etiology of ALF in the United States and Europe\(^{(8)}\).

DILI has been attributed to either intrinsic hepatotoxicity or idiosyncratic reaction to the drug\(^{(10)}\). While the former is predictable, dose dependent, and reproducible in preclinical models, the latter occurs without obvious dose dependency and in an unpredictable fashion. Drug idiosyncrasy has been further classified as either immunoallergic or metabolic phenotype\(^{(10)}\). The immunoallergic reaction denotes a hyperactive immune response to the drug or metabolites, seen more commonly in female patients and occurring 2–10 weeks

**FIG. 1.** Photomicrograph of post-mortem liver biopsy specimen of patient with pirfenidone related acute liver failure. (A) Hematoxylin and eosin staining showing centrilobular confluent hepatic necrosis and bridging necrosis (magnification \(×100\)), (B) reticulin staining highlighting reticulin collapse (magnification \(×100\)), and (C) Masson trichrome stain (pale blue) (magnification \(×100\)). (D) Centrilobular area also showed accumulation of Kupffer cells and macrophages containing lipofuscin-like brown-colored pigment and few surviving, swollen, and multivacuolated hepatocytes (hematoxylin and eosin; magnification \(×400\)). (E) Most of the portal tracts showed minimal to mild inflammatory infiltrate except for a few containing lymphocytes admixed with a few eosinophils (hematoxylin and eosin; magnification \(×400\)).
after drug intake; the reaction includes presentation with systemic symptoms, such as fever, eosinophilia, rash, and lymphadenopathy, the presence of autoantibodies, and prompt improvement after drug withdrawal. On the other hand, metabolic idiosyncrasy has a variable presentation without any gender predilection and fewer systemic symptoms; it occurs as a possible drug to drug interaction, has rare association with peripheral eosinophilia, and shows mild or no eosinophilia on liver histology. Our case had an abrupt presentation 1 month after drug exposure, without any fever, rash, eosinophilia, or drug-dose relationship, suggestive of metabolic idiosyncratic reaction.

Among the etiologies of DILI-ALF, antibiotics and antitubercular drugs are the most common cause, followed by herbal supplements, anti-epileptics, and non-steroidal anti-inflammatory drugs. Pirfenidone is a pyridine derivative with anti-inflammatory and antifibrotic properties; it inhibits collagen formation by halting transforming growth factor β synthesis and decreasing fibroblast proliferation. Initially used as an anthelminthic and antipyretic, it is currently approved as an antifibrotic drug for use in patients with IPF. It has also been shown to reduce liver fibrosis in animal models and improve fibrosis in patients with chronic hepatitis C. In large randomized control trials, hepatotoxicity has been reported in about 4% of patients, with mild to moderate asymptomatic serum aminotransferase elevations requiring termination of the drug in up to 1% of cases. Elevated transaminases between 3 and 5 times ULN with symptoms and more than 5 times ULN with or without symptoms are the general stopping rules. Despite elevation of liver enzymes during therapy, clinically significant liver injury leading to ALF has never been reported. Here, we described an unusual case of ALF related to pirfenidone.

The pathogenesis of idiosyncratic DILI is not well understood. The drug or its metabolite may cause direct cellular stress or oxidative stress or may form neoantigens after haptenization. These may lead to mitochondrial permeability transition, further activating the pathways of apoptosis, generation of damage-associated molecular patterns, and subsequent immune activation and damage. In this case, it is interesting to note the DILI due to pirfenidone because pirfenidone inhibits tumor necrosis factor α production, has anti-inflammatory properties, and is presumed to be a cellular protective agent. Pirfenidone is predominantly metabolized by the hepatic cytochrome P450 (CYP) 1A2 enzyme system to yield inactive 5-carboxypirfenidone, and 80% of the dose is excreted in urine within 24 hours. Toxicity has been linked to drug interactions with CYP1A2 inhibitors. In our case, it is possible that the levodopa/carbidopa and pirfenidone combination might have precipitated the fatal liver injury. However, an interaction between these two has not been reported; levodopa/carbidopa is largely metabolized by monoamine oxidases and has not been shown to inhibit CYP enzymes. Therefore, this report warrants further study.

The clinical presentation of idiosyncratic DILI-ALF is nonspecific and is like any viral illness that is followed by jaundice, coagulopathy, and encephalopathy. The diagnosis is often one of exclusion, based on a high index of suspicion and ruling out other causes of liver dysfunction. There is no single gold standard for the diagnosis, but the armamentarium includes good clinical history, workup for alternative etiologies, causality assessment scores, and liver histology. Recently, multiple molecular markers that suggest DILI have been proposed; examples include microRNA-122 in acetaminophen overdose, high mobility group box-1 and cytokeratin-18 in the prediction of early liver injury, macrophage colony-stimulating factor receptor 1 in flupirtine toxicity, and osteopontin levels or glycodeoxycholic acid in predicting severe DILI. Certain autoantibodies, such as anti-CYP1A2 in dihydralazine DILI, anti-CYP3A in anticonvulsant DILI, anti-CYP2E1 in halothane hepatitis, and anti-isoniazid antibodies in isoniazid-induced ALF, have been proposed. Blood pyrrole–protein adducts have been proposed for pyrrolizidine-DILI. Also, genome-wide association studies have linked certain human leukocyte antigen (HLA) alleles
with DILI; examples include HLA-DRB1*1501 in amoxicillin–clavulanate and HLA-A*33:01 for a cholestatic or mixed pattern of DILI. The index case was diagnosed as DILI-ALF based on history, exclusion of other etiologies as per American College of Gastroenterology guidelines, temporal correlation, postmortem liver biopsy findings, and RUCAM score.

Liver biopsy is not essential for the diagnosis of DILI, but it is indicated when autoimmune hepatitis (AIH) is a differential diagnosis or immunosuppressive therapy is contemplated. Liver biopsy is also indicated when there is persistent rising liver function tests, signs of liver failure even after dechallenge, or lack of 50% reduction in peak ALT level at 30-60 days after the onset in cases of HC-DILI or if the peak ALP level has not fallen by >50% at 180 days in cases of CS-DILI after drug withdrawal. Liver biopsy is also considered where continued use of the drug is expected or liver functions remain altered beyond 180 days. Liver biopsy findings are generally classified into one of the 18 patterns described. It is important to note that none of the findings are diagnostic for DILI. A study from the DILI Network reported the most common patterns of DILI as acute (21%); chronic hepatitis (14%), acute (9%), and chronic cholestasis (10%); and CS hepatitis (29%). The patients with HC presentation had more severe inflammation, necrosis, and apoptosis and more frequent lobular disarray, rosette formation, and hemorrhage than those with CS presentation. The patients with CS-DILI had more bile plugs and duct paucity. Severe or fatal DILI has been shown to have higher degrees of necrosis, fibrosis, ductular reaction, and microvesicular steatosis, whereas granulomas and eosinophils were more common in mild DILI. Recently, a study attempted to differentiate DILI from AIH on histology. The HC type of DILI had more prominent intra-acinar lymphocytes and canalicular cholestasis, whereas AIH had more severe interface hepatitis, focal necrosis, and portal inflammation. AIH also had more portal and intra-acinar plasma cells, rosette formation, and emperipolysis compared to DILI. In the present case, liver biopsy showed massive centrilobular and bridging necrosis and vacuolated hepatocytes associated with elevated lactate and lactate dehydrogenase, perhaps due to mitochondrial injury and mild portal inflammation possibly resulting from immune-mediated damage. Relatively mild eosinophilia in the liver biopsy in our case was consistent with the reported cases of fatal DILI.

Treatment options for DILI-ALF include drug withdrawal, intensive care support, N-acetyl cysteine, and LT. Although most idiosyncratic DILIs improve after drug withdrawal, failure to recover after severe liver injury (DILI-ALF) is unlikely. N-acetyl cysteine has been shown to improve transplant-free survival in adults with DILI-ALF. However, the results are contradictory in the pediatric population and equivocal in a prospective cohort study. LT is the only definitive treatment for those with poor prognosis. Of the 95 patients with DILI-ALF listed for transplant between 2000 and 2013 in the United States, 22.1% (n = 21) died, 11.5% (n = 11) survived, and 66.3% (n = 63) were transplanted, with a post-transplant survival rate of 92.1% at week 3. Outcomes depend on the extent of injury, the number of organ failures at admission, quality of intensive care, and availability of salvage therapies. Our case had poor prognostic factors, including high model for end-stage liver disease, poor King’s College Hospital criteria, older age, malnutrition, grade III encephalopathy, cerebral edema, and renal failure at admission followed by sepsis and multiorgan failure. Recently, the ALF study group has proposed prognostic criteria based on the grade of hepatic encephalopathy, etiology, use of vasopressors, bilirubin, and international normalized ratio values. As per the criteria, our case had 9% probability of spontaneous survival. Therefore, such patients should be evaluated for LT early in their assessment.

Conclusion

Idiosyncratic DILI-related ALF is rare and carries high mortality. LT should be considered early in its course. Characterization, reporting, monitoring, and labeling of pirfenidone-related hepatotoxicity is vital, given its common use in IPF. However, further studies are warranted to elucidate the exact mechanisms underlying DILI from pirfenidone.

REFERENCES

1) Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065-2076.
2) Macías-Barragan J, Sandoval-Rodríguez A, Navarro-Partida J, Armendáriz-Borunda J. The multifaceted role of pirfenidone and its novel targets. Fibrogenesis Tissue Repair 2010;3:16.
3) García L, Hernandez I, Sandoval A, Salazar A, García J, Vera J, et al. Pirfenidone effectively reverses experimental liver fibrosis. J Hepatol 2002;37:797-805.
4) Armendáriz-Borunda J, Islas-Carbajal MC, Meza-García E, Rincón AR, Lucano S, Sandoval AS, et al. A pilot study in patients with established advanced liver fibrosis using pirfenidone. Gut 2006;55:1663-1665.

5) Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89:806-815.

6) Temple R. Hy’s law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf 2006;15:241-243.

7) Lo Re V 3rd, Haynes K, Forde KA, Goldberg DS, Lewis JD, Carbonari DM, et al. Risk of acute liver failure in patients with drug-induced liver injury: evaluation of Hy’s law and a new prognostic model. Clin Gastroenterol Hepatol 2015;13:2360-2368.

8) Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ, Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014;109:950-966.

9) Fontana RJ, Seeff LB, Andrade RJ, Bjornsson E, Day CP, Serrano J, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:730-742.

10) Kullak-Ublick GA, Andrade RJ, Merz M, End P, Benesic A, Gerbes AL, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut 2017;66:1154-1164.

11) United States National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases. Pirfenidone. https://livertox.nih.gov/Pirfenidone.htm. Accessed November 20, 2017.

12) Fontana RJ, Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. Gastroenterology 2014;146:914-928.

13) McGill MR, Jaeschke H. Mechanistic biomarkers in acetaminophen-induced hepatotoxicity and acute liver failure: from preclinical models to patients. Expert Opin Drug Metab Toxicol 2014;10:1005-1017.

14) Antoine DJ, Dear JW, Lewis PS, Platt V, Coyle J, Masson M, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. Hepatology 2013;58:777-787.

15) Clarke JI, Dear JW, Antoine DJ. Recent advances in biomarkers and therapeutic interventions for hepatic drug safety – false dawn or new horizon? Expert Opin Drug Saf 2016;15:625-634.

16) Gao H, Ruan JQ, Chen J, Li N, Ke CQ, Ye Y, et al. Blood pyrrole-protein adducts as a diagnostic and prognostic index in pyrrolizidine alkaloid-hepatic sinusoidal obstruction syndrome. Drug Des Devel Ther 2015;9:4861-4868.

17) Donaldson PT, Daly AK, Henderson J, Graham J, Pirmohamed M, Bernal W, et al. Human leukocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury. J Hepatol 2010;53:1049-1053.

18) Grove JL, Aithal GP. Human leukocyte antigen genetic risk factors of drug-induced liver toxicity. Expert Opin Drug Metab Toxicol 2015;11:395-409.

19) Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, et al.; Drug-Induced Liver Injury Network (DILIN). Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology 2014;59:661-670.

20) Suzuki A, Brunnt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 2011;54:931-939.

21) Bjornsson E, Kalaitzakis E, Olsson R. The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury. Aliment Pharmacol Ther 2007;25:1411-1421.

22) Lee WM, Hyun LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al.; Acute Liver Failure Study Group. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856-864, 864.e1.

23) Squires RH, Dhawan A, Alonso E, Narkevicz MR, Shneider BL, Rodriguez-Baez N, et al.; Pediatric Acute Liver Failure Study Group. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. Hepatology 2013;57:1542-1549.

24) Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, et al. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. Ann Intern Med 2016;164:724-732.

25) Reddy KR, Ellerbe C, Schilsky M, Stravitz RT, Fontana RJ, Durlakski V, et al.; Acute Liver Failure Study Group. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the US. Liver Transpl 2016;22:505-515.