Asian Journal of Medicine and Health Sciences Vol 6 Issue 2, November 2023

CASE REPORT

Idiosyncratic Drug-induced Liver Injury: A Diagnosis Beyond Simplicity.

Leong Hui Shan[1*], Thirugnanasampanthar Terpari[2], Wahinuddin Sulaiman[1]

[1]Faculty of Medicine, Royal College of Medicine Perak, Universiti Kuala Lumpur, Malaysia.
[2]Department of Medicine, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia.

Corresponding Author
Dr Leong Hui Shan
Department of Medicine, Faculty of Medicine,
Royal College of Medicine Perak, Universiti Kuala Lumpur,
No 3, Jalan Greentown, 30450 Ipoh, Perak, Malaysia.
Email: hsleong@unikl.edu.my

Submitted: 25/05/2023. Revised edition: 03/07/2023. Accepted: 28/09/2023. Published online: 01/11/2023

Abstract

Idiosyncratic drug-induced liver injury is a relatively uncommon adverse drug reaction but can be potentially fatal. The clinical spectrum of this liver disorder can range from an asymptomatic biochemical derangement to a life-threatening fulminant liver failure. Due to its unpredictable nature, the diagnosis of idiosyncratic drug-induced liver injury is challenging and demands a high index of suspicion. There is no definitive diagnostic marker and hence, it is mandatory to exclude other aetiologies of liver damage. While certain drugs are well-established to cause idiosyncratic hepatotoxicity, there remains a large group of agents which are yet to be identified as culprits. We report a case of probable idiosyncratic drug-induced liver injury that evolved after a tooth extraction in a young man in whom the diagnostic evaluation was complicated due to simultaneous exposure to multiple agents and incomplete information related to the drug.

Keywords: *acute liver failure, diclofenac, idiosyncratic drug-induced liver injury, mepivacaine, tooth extraction.*

Introduction

Drug-induced liver injury (DILI) is defined as liver injury caused by exposure to medications (prescribed or over-the-counter), herbal and dietary supplements (HDS), or other xenobiotics that result in a variable degree of hepatic tissue damage and dysfunction which is not attributed to other aetiologies [1]. The exact epidemiological data of DILI is difficult to determine mainly due to underdiagnosis and underreporting. It is evident that DILI has emerged as the leading cause of acute liver failure in Western countries and has also become increasingly common in Asia [2]. In China, about 20% of the admissions for acute liver injury are DILI-related and the rising incidence of DILI is attributed to widespread consumption of traditional Chinese medicines and HDS which can be easily obtained over-the-counter [3]. A retrospective study analysing the data between the years 2000 and 2017 in Malaysia also indicated that the incidence of hepatic adverse drug reaction reporting had increased significantly over 18 years from 0.26 to 9.45 per million population [4].

Several mechanisms of hepatotoxicity have been implicated in DILI [5,6]. The harmful effects can be directly caused by a parent drug or by its reactive metabolites. An attack on the hepatocytes will compromise the cellular integrity leading to DNA damage and dysfunction. Certain reactive metabolites can interact with hepatic proteins and form antigenic drug-protein adducts, which subsequently trigger an immune response resulting in liver injury. Some drugs may mediate liver damage via a hypersensitivity reaction.

The clinical manifestations of DILI are highly variable and it often mimics other hepatobiliary diseases [7]. Hence, the diagnosis of DILI relies on a high degree of suspicion. Here, we highlight a case of a previously healthy young man who developed rapid onset of acute liver failure after a dental procedure and demonstrated recovery of liver function within 72 hours after the onset. This clinical course was suggestive of DILI. However, the determination of the actual offending agent was proven to be difficult.

Case report

A 34-year-old man, previously well with no underlying co-morbidities, developed toothache for one week. Despite taking regular analgesics which he purchased from a local pharmacy, the problem persisted and he had a tooth extraction on the day of admission. The procedure was uneventful. He remained alert and was able to ride his motorcycle back to his house. However, a few hours after he arrived home, his family member noticed that he became restless and at times turned blank with little response. He also had two episodes of vomiting. Subsequently, he was found unconscious in his bed, presumed had a seizure. There was no history of drug allergy, ethanol consumption, substance use or any high risk behaviour. An immediate ambulance call to the nearest healthcare facility was made. Initial assessment showed that he was drowsy and hypotensive. Coffee ground aspirate, prolonged INR, and renal impairment were noted. He was suspected to have an upper gastrointestinal bleed and was referred for endoscopy.

In the tertiary hospital (12 hours after the dental procedure), he remained confused, slow to response, and could not recall the events that happened at home. There was no fever, haematemesis, or melaena. His vital signs, urine output, and blood glucose were normal and stable. Besides the altered mental status, the other physical examination was unremarkable. Blood tests revealed abnormal and rapidly rising liver enzymes within a day. Aspartate transaminase (AST) escalated from 412 U/L (Normal: 5-34 U/L) to 1944 U/L and reached a peak of 4552 U/L. Alanine transaminase (ALT) increased from 250 U/L (Normal: 0-55 U/L) and peaked at 3351 U/L. Serum albumin, alkaline phosphatase (ALP), and initial bilirubin were normal. INR and aPTT were prolonged (2.18 and 51.9 second respectively). Serum ammonia was high (90 µmol/L). Blood counts revealed leucocytosis (21.8 x 10^9/L) with neutrophilia (90.4%) and thrombocytopaenia (113 x 10^9/L). Serum creatinine was elevated (164 µmol/L) with reduced eGFR (46

mL/min/1.73m2). Abdominal ultrasound reported thickened gallbladder wall but no evidence of biliary obstruction or hepatic lesions. Upper endoscopy showed pangastroduodenitis. No active bleeding was found. CT scan of brain, cardiac assessment, and imaging of the chest were all normal.

His clinical manifestations and biochemical abnormalities were consistent with acute liver failure (ALF) with multiorgan involvement (evidence of liver damage, hepatic encephalopathy, coagulopathy, hyperammonaemia, underlying sepsis, acute kidney injury, initial circulatory instability with possible upper gastrointestinal bleeding). Drug toxicity was considered the likely underlying pathology. The local anaesthetic agent used during the tooth extraction was verified to be Mepivacaine Hydrochloride 2%. However, the details of the analgesics were deficient. He could not recall the name of the medicine. It was acquired over-the-counter without a prescription. He took one tablet three times a day for one week and the last dose was ingested the night before the tooth extraction.

Further investigations to exclude other aetiologies of ALF were carried out. The paracetamol level in the plasma was undetectable. Hepatitis B and C screening was negative. However, hepatitis A serology was not done. He was treated with intravenous fluid therapy, fresh frozen plasma, *N*-acetylcysteine infusion, syrup lactulose, intravenous ceftriaxone and intravenous esomeprazole. Daily monitoring of liver function was done.

His final diagnosis was probable idiosyncratic drug-induced liver injury. Considering the history of exposure and the temporal relationship to the clinical events, both a non-steroidal anti-inflammatory drug (NSAID), possibly diclofenac, and Mepivacaine could be implicated. Throughout the seven days of admission, his condition was stable. The encephalopathy resolved within three days. He started to developed mild jaundice with elevation of serum bilirubin (52.3 µmol/L) on day three which subsequently normalized. Both transaminases began to decline significantly from the peak level with AST reaching 119 U/L and ALT at 657 U/L after five days. Other blood parameters normalized prior to discharge. Subsequent monitoring of liver function test would be continued in the nearest healthcare facility.

Discussion

Drug-induced liver injury (DILI) is generally classified into intrinsic and idiosyncratic. While intrinsic DILI has a consistent dose-toxicity relationship with a predictable latency and clinical course, idiosyncratic DILI on the contrary, is unpredictable in these aspects and only affects susceptible individuals [8]. Owing to its peculiar nature, the occurrence of idiosyncratic DILI is often unexpected and hence poses a great challenge in its diagnosis. Certain risk factors have been considered to predispose an individual to idiosyncratic DILI which include host characteristics (age, gender, pregnancy, existing liver disease), lifestyle (smoking, ethanol consumption), and pharmaceutical factors (dosage, pharmacokinetics, drug interaction) [9].

Suspicion of DILI arises when an abnormal liver function test is recognized, whether it is clinically apparent or not. By expert consensus, significant drug-induced liver damage would include one of the following thresholds: (a) ALT $\geq$ 5x upper limit of normal (ULN) or (b) ALT $\geq$ 3x ULN plus total bilirubin $\geq$ 2x ULN or (c) ALP $\geq$ 2x ULN plus increase of gamma-glutamyl-transferase after excluding bone pathology [10]. In suspected DILI, further evaluation with comprehensive clinical history, documentation of the drug-related details, time of exposure, the onset of liver biochemical abnormalities, and the course of liver damage is of paramount importance [9]. Certain pitfalls may be encountered in gathering information such as lack of record regarding the type, dosage and duration of medication, polypharmacy, undisclosed history of over-the-counter medication or unregistered HDS [11]. These pitfalls were clearly reflected in our patient

as he was exposed to two medications prior to the onset of the ALF and one of them had no proper record.

As idiosyncratic DILI is further categorized into hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$), and mixed ($2 > R < 5$) based on the pattern of liver injury, calculation of the R value usually follows once DILI is considered a possibility [12]. The R value is defined as measured ALT/ULN of ALT divided by measured ALP/ULN of ALP. By determining the pattern of liver injury, it helps the clinician to further plan the diagnostic work-up with a more specific focus to rule out other causes as DILI remains a diagnosis of exclusion. Other differential diagnoses which may give rise to hepatocellular injury include viral hepatitis, shock liver, acute Budd-Chiari syndrome, autoimmune hepatitis, and ethanol-related liver disease while cholestatic DILI may mimic biliary obstruction and immune-mediated biliary diseases [11]. Besides the laboratory investigations (e.g., viral hepatitis serology, relevant autoantibody panel) and hepatobiliary imaging which are the usual modalities implicated in the diagnostic approach, liver biopsy may also play a role especially when autoimmune hepatitis remains a competing cause or the dechallenge is partial or negative after withdrawal of the offending agent [13].

In current practice, the final diagnosis of DILI is based on clinical judgement and expert opinion after careful evaluation and exclusion of other aetiologies of liver injury [7,9,11]. There are several tools which can facilitate the causality assessment in suspected DILI to aid in the diagnosis [10]. Roussel Uclaf Causality Assessment Method (RUCAM) is the most well-structured and validated scoring system that is widely applied for this purpose [14]. Following the parameters in this method, it allows a systematic analysis and subsequently generates a grade which will categorize the DILI into highly probable (>8), probable (6–8), possible (3–5), unlikely (1–2) or excluded (<0). By applying RUCAM in our patient, we derived a score of 8 (probable) for the analgesic, presumed diclofenac and 5 (possible) for Mepivacaine.

It is crucial to determine the offending agent in DILI in order to avoid future exposure. The American College of Gastroenterology (ACG) has published an extensive list of drugs which are well-established to cause idiosyncratic DILI [9]. In Western countries, antibiotics and NSAIDs are the main offenders while in Asia, anti-tuberculous drugs and traditional medications top the list [2]. With the continuous development of new drugs and mushrooming of HDS, it is expected more products would be implicated in DILI.

As diclofenac is one of the most frequently used and easily available analgesics, it is possible our patient was exposed to this particular NSAID. Researchers had demonstrated that diclofenac represents one of the commonest NSAID linked to clinically significant idiosyncratic hepatotoxicity and the pattern of injury is mostly hepatocellular [15]. The time of onset of liver injury varies and can range from less than a week to more than a year following initiation of diclofenac [16]. Mepivacaine is an amide-based local anaesthetic which is regularly used in dental procedure. Hepatotoxicity has not been labeled as a side effect of amide-based local anaesthetics and reporting on clinically apparent Mepivacaine-related DILI remains scarce [17]. However, a study by Gheisari et al had highlighted the adverse hepatic effect of Mepivacaine on mice. In this study, Mepivacaine administered via oral mucosa had resulted in a significant increase in liver enzymes in both mice with paracetamol-induced liver failure and without liver failure, when compared with other amide-based local anaesthetics (lidocaine, prilocaine with felypressin, articaine) [18]. Further research on human subjects is highly anticipated. In addition, there were several case reports of DILI associated with Bupivacaine when it was used as post-operative surgical site infusion for pain relief and intra-articular injection after total knee arthroplasty indicating possible idiosyncratic reaction with amide-based local anaesthetics [19,20].

The fundamental principles of the therapeutic approach in DILI include immediate discontinuation of the offending agent once identified, avoiding repeat usage of the drug, supportive treatment with close monitoring of liver biochemistry, initiation of a hepatoprotective or anticholestatic agent when appropriate depending on the pattern of liver injury, and consideration of liver transplant if indicated [21]. The clinical outcome is usually favourable with the majority of cases recovering spontaneously.

Conclusion

The incidence of DILI is on the rise. However, the process in establishing a diagnosis of idiosyncratic DILI is complex and the determination of the offending agent is not always straightforward. Current existing clinical practice guidelines and databases on DILI are helpful. Future research is important to further overcome the challenges in DILI diagnosis.

Conflict of Interest and financial disclosures
None.

References

[1]. Suk KT, Kim DJ. Drug-induced liver injury: present and future. *Clinical and Molecular Hepatology.* 2012; 18(3):249-257. doi:10.3350/cmh.2012.18.3.249.

[2]. Jayaraman T, Lee YY, Chan WK, Mahadeva S. Epidemiological differences of common liver conditions between Asia and the West. *JGH Open.* 2019; 4(3):332-339. doi:10.1002/jgh3.12275.

[3]. Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, Cong WM *et al*; Drug-induced Liver Injury (DILI) Study Group; Chinese Society of Hepatology (CSH); Chinese Medical Association (CMA). CSH guidelines for the diagnosis and treatment of drug-induced liver injury. *Hepatology International.* 2017; 11(3):221-241. doi:10.1007/s12072-017-9793-2.

[4]. Lee FY, Wong H, Chan H, Mohamed Ali N, Abu Hassan MR, Omar H *et al*. Hepatic adverse drug reactions in Malaysia: An 18-year review of the national centralized reporting system. *Pharmacoepidemiology & Drug Safety.* 2020; 29(12):1669-1679. doi:10.1002/pds.5153

[5]. Serras AS, Rodrigues JS, Cipriano M, Rodrigues AV, Oliveira NG, Miranda JP. A Critical Perspective on 3D Liver Models for Drug Metabolism and Toxicology Studies. *Frontiers in Cell Developmental Biology.* 2021; 9:626805. doi:10.3389/fcell.2021.626805

[6]. Lisi DM. Drug-Induced Liver Injury: An Overview. *US Pharmacist.* 2016; 41(12):30-34.

[7]. 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(6):1154-1164. doi:10.1136/gutjnl-2016-313369.

[8]. Roth RA, Ganey PE. Intrinsic versus idiosyncratic drug-induced hepatotoxicity--two villains or one?. *The Journal of Pharmacology and Experimental Therapeutics.* 2010; 332(3):692-697. doi:10.1124/jpet.109.162651.

[9]. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *The American Journal of Gastroenterology.* 2021; 116(5):878-898. doi:10.14309/ajg.0000000000001259.

[10]. Marrone G, Vaccaro FG, Biolato M, Miele L, Liguori A, Araneo C *et al*. Drug-induced

liver injury 2017: the diagnosis is not easy but always to keep in mind. *European Review for Medical and Pharmacological Sciences.* 2017; 21(1 Suppl):122-134.

[11]. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guideline Panel: Chair:; Panel members; EASL Governing Board representative:. EASL Clinical Practice Guidelines: Drug-induced liver injury. *Journal of Hepatology.* 2019; 70(6):1222-1261. doi:10.1016/j.jhep.2019.02.014.

[12]. Brennan PN, Cartlidge P, Manship T, Dillon JF. Guideline review: EASL clinical practice guidelines: drug-induced liver injury (DILI). *Frontline Gastroenterology.* 2022; 13(4):332–336. doi:10.1136/flgastro-2021-101886.

[13]. Andrade RJ, Robles-Díaz M. Diagnostic and prognostic assessment of suspected drug-induced liver injury in clinical practice. *Liver International.* 2020; 40(1):6-17. doi:10.1111/liv.14271.

[14]. Teschke R. Idiosyncratic DILI: Analysis of 46,266 Cases Assessed for Causality by RUCAM and Published From 2014 to Early 2019. *Frontiers in Pharmacology*. 2019; 10:730. doi:10.3389/fphar.2019.00730.

[15]. Sriuttha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review of Randomized Controlled Trials. *International Journal of Hepatology*, 2018; 2018:5253623. DOI:10.1155/2018/5253623.

[16]. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. 2012-. Diclofenac. [Updated 2017 Dec 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547953/

[17]. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Amide Local Anesthetics. [Updated 2017 Jul 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547905/

[18]. Gheisari R, Arasteh P, Estakhri F, Eatemadi H, Jamshidi A, Javad Khoshnoud M *et al*. The Safety and Side Effects of Amide-Based Local Anesthetics in Rats with Acetaminophen-Induced Hepatic Injury. *Iranian Journal of Medical Sciences.* 2020; 45(5):377-382. doi:10.30476/ijms.2020.72596.0.

[19]. Chintamaneni P, Stevenson HL, Malik SM. Bupivacaine drug-induced liver injury: a case series and brief review of the literature. *Journal of Clinical Anesthesia.* 2016; 32:137-141. doi:10.1016/j.jclinane.2016.01.035.

[20]. Lee JE, Kwak KH. A liver transplant recipient with possible bupivacaine-induced liver injury caused by intra-articular injection after total knee arthroplasty: A case report. *Medicine (Baltimore).* 2018; 97(38):e12481. doi:10.1097/MD.0000000000012481.

[21]. Li M, Luo Q, Tao Y, Sun X, Liu C. Pharmacotherapies for Drug-Induced Liver Injury: A Current Literature Review. *Frontiers in Pharmacology.* 2022; 12:806249. doi:10.3389/fphar.2021.806249.