Case Report

Drug-induced Liver Injury: A Rare Complication of Commonly Prescribed Antibiotics

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Abstract

Background: Drug-induced liver injury (DILI) is an unusual manifestation of hepatic disease and a crucial differential diagnosis because of its complexity to identify. The clinical appearance of DILI can range widely, presenting as clinically silent alterations in hepatic biochemistry or as an abrupt onset of liver illness or liver failure with symptoms. The main causative agents that have been implicated are antibiotics like penicillin and cephalosporin, as well as non-steroidal anti-inflammatory drugs, anti-epileptic drugs, and complementary and alternative medicine (CAM).

Case Report: Here, we report a case of an 87-year-old male patient who was diagnosed with cholestatic hepatitis after receiving a ten-day therapy of amoxicillin-clavulanate and clindamycin for a peritonsillar abscess. Various other possible causes of hepatic injury were ruled out, such as infections, autoimmune hepatic diseases, and primary biliary tract diseases. DILI was approved to be the most probable diagnosis. Given that the patient's cholestasis deteriorated further, prednisone and ursodeoxycholic acid were administered concurrently. Following 4 weeks of therapy, the patient's symptoms and laboratory findings were improved significantly. According to our outcomes, this therapy was proven to be quite effective. Our purpose in presenting this case of DILI is to raise awareness about an uncommon side effect of widely prescribed medications.

Conclusion: Despite being a rare diagnosis, drug-induced liver injury (DILI) is often overlooked in clinical practice. Several reasons have been proposed; however, there is currently no clear link between drugs, risk factors, and the causes of DILI.

Key words: amoxicillin-clavulanate, clindamycin, antibiotic-induced hepatitis, thrombocytopenia, immunoglobulin G

Introduction

Drug-induced liver injury (DILI) is categorised based on the pathophysiological mechanisms as intrinsic, which is dose-dependent with a hepatotoxic reaction that manifests itself hours to days upon exposure, or idiosyncratic, which is unrelated to dose, route of administration, and duration of treatment and has a variable period of onset,

ranging from weeks to months, and an unpredictable course. (Hosack T, 2023), (Wettasinghe I., 2023) According to the nature of hepatic damage seen in idiosyncratic DILI, this is further categorised into hepatocellular, cholestatic, or mixed, which is strongly associated with the pattern of liver enzyme abnormalities. (Hosack T, 2023) DILI is considered a diagnosis of exclusion. (Moole, 2015) For establishing the cause of hepatotoxicity, certain etiologic factors need to be excluded, like viral and autoimmune hepatitis, alcohol, biliary tract disorders, haemodynamic factors (hypoxaemia and ischaemia), prescribed and over-the-counter drugs, and gallstones. (Moole, 2015), (deLemos, 2016) Old age, male gender, and receiving prolonged therapeutic schemes are potential risk factors associated with DILI. (Appiah, 15(1), e33445. https://doi.org/10.7759/cureus.33445)

The incidence rate of DILI is estimated at around 1/10,000–1/100,000 people per year and is correlated to the country and organisation that led the study. (J, 2021)

Antibiotics are a prevalent risk factor for DILI because of their widespread use. (Mdsafe, 2012) According to Spanish and US DILI registry data, amoxicillin/clavulanate appeared to be the most prevalent cause of idiosyncratic DILI. (J, 2021) Amoxicillin-clavulanate is the most frequently prescribed drug implicated in drug-induced liver injury, with liver damage occurring within three to four weeks following initial therapy. (Herrero-Herrero J. G.-A., 2010) (Goyal L, 2022) The cholestatic variant is strongly associated with amoxicillin-clavulanate, even though the hepatocellular and mixed variants could be observed. (Herrero-Herrero J. G.-A., 2010) It predominates in older male individuals and is characterised by a gradual resolution following drug withdrawal. (deLemos, 2016), (Ferreira I, 2020) A significant percentage of cholestatic types of liver damage are benign, but 10% of them have the potential to progress into cirrhosis. (Ferreira I, 2020) The majority of amoxicillin-clavulanic-induced liver injury cases follow a mild-to-moderate disease course and achieve full remission. Certain patients may experience severe acute liver failure, particularly if they have multiple comorbidities or have been exposed repeatedly. (Appiah, 15(1), e33445. https://doi.org/10.7759/cureus.33445)
Moreover, the literature only reports a limited number of DILI cases associated with systemic clindamycin therapy. (Moole, 2015) Two main types of clindamycin-induced hepatotoxicity have been identified: a temporary transamineamia and an abrupt idiosyncratic hepatotoxicity, manifesting 1 to 3 weeks post-therapy. Several apoptotic pathways have been identified in cases of clindamycin-induced liver injury. (Moole, 2015) In general, antibiotic-induced liver injury has a good prognosis. Notwithstanding, those presented with jaundice have a 10% mortality risk due to liver failure and the potential necessity of liver transplantation. (S., 2017)

Herein, we report a case of acute hepatitis accompanied by immune-mediated thrombocytopenia contributed to antibiotic-induced liver injury. We want to emphasise that even after antibiotic therapy has been completed, the acute clinical presentation of DILI can lead to focusing on common causes like obstruction and malignancy, potentially misleading the differential diagnosis.

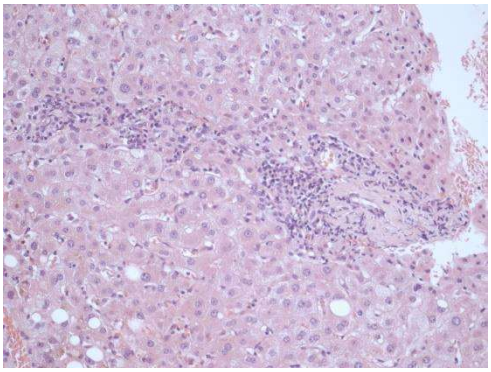
Case Report

An 87-year-old male patient with a medical history of arterial hypertension, non-smoking, no alcohol consumption, and no allergies was presented to the emergency department due to a 1-week history of painless jaundice, hyperpigmentation of urine, and pruritus that started 2 days ago. There were no references to recent travel abroad. Neither the consumption of mushrooms, alcohol, nor herbs was mentioned. However, two weeks ago, the patient presented to an emergency department with a 3-day history of worsening pharyngitis and unilateral earache. He was

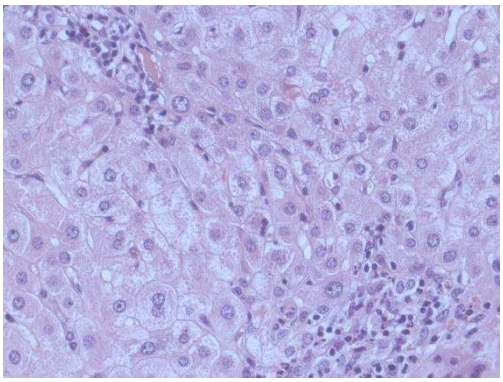
diagnosed with a unilateral peritonsillar abscess and managed with drainage. Culture of the abscess aspirate was performed, and Streptococcus species was isolated. The patient declined to be admitted to the hospital and received at-home treatment with antibiotics, including amoxicillin-clavulanic acid (1000 mg 1x3 for 2 days and then 1000 mg 1x2 for 10 days), clindamycin (300 mg 1x3 for 3 days and then 1x4 for 10 days), NSAIDs, and cortisone (16 mg 2x1 for 4 days and then 1x1 for 6 days).

Upon initial assessment, he was alert, afebrile, and clinically stable. The evaluation of the cardiovascular system indicated irregular pulses and normal heart sounds without murmurs. An examination of the abdomen showed no signs of pain, a soft and depressible abdomen, and normal bowel sounds. The patient had generalised jaundice, predominantly on the face, chest, and abdomen. Icterus of the sclera was quite remarkable without any other sign indicative of chronic liver disease. Initial blood tests revealed the following: white blood cell counts $5.6x10^3/\mu L$ (reference range: 4.6-10.2 $x10^3/\mu L$), Hgb 15.70g/dL (reference range: 12-18), Hct 47% (reference range: 37-52%), platelets 279 $x10^3/\mu L$ (reference range 130-400 $x10^3/\mu L$), ALT 578 IU/L (reference range: <55); ALP 335 IU/L (reference range: 40-150); GGT 657 IU/L (reference range: 12-64); total bilirubin 10.70 mg/dL (reference range: 0.20-1.00 mg/dL); direct bilirubin 3.64 mg/dL (reference range: 0.10-0.50 mg/ dL). So, the initial liver biochemistry tests revealed a mixed pattern of liver injury.

He was initially admitted to the Department of General Surgery. Given the possibility of cholecystitis, on day one of his admission, intravenous antibiotics started, including metronidazole and ciprofloxacin. Abdominal and chest X-rays were unremarkable. The liver and gallbladder/biliary tract ultrasound showed diffuse heterogeneity of the hepatic parenchyma without evidence of dilatation or obstruction of the intra- and extrahepatic bile ducts. On day 2, the repeated liver biochemistry tests showed a cholestatic pattern of liver injury (ALT 229 IU/L, ALP 486 IU/L, GGT 462 IU/L, total bilirubin 30.40 mg/dL, direct bilirubin 15 mg/dL).



1a.



1b.

(Figures 1a & 1b). Inflamed portal tract of the liver. Irregular epithelium of a bile duct infiltrated by lymphocytes and neutrophils, eosinophilic leukocytes, and mild cholestasis, due to drug-induced injury. (HEX200 ,HEX400)

At that time, having an unremarkable upper abdominal US along with worsening liver function tests and the unexplained cholestasis, an upper abdominal MRI, and an MRCP were considered. Three simple hepatic cysts, measuring a few millimetres, were found. There were no filling defects in either the extrahepatic or intrahepatic biliary tree. The blood and urine cultures taken on the first day came back negative.

Following 2 days of hospitalisation, the patient was transferred to the Internal Medicine Department for additional investigation. Firstly, the antibiotic therapy was discontinued since the initial presumed diagnosis of cholecystitis was ruled out, and methylprednisolone was started intravenously (S: 16 mg 1x2 per day). Antihistamines were provided on-demand for the control of pruritus. New-onset atrial fibrillation (AF) was identified during the first few days of his hospitalisation, and oral anticoagulant therapy with apixaban was initiated. Further derangement of liver biochemistry was observed in daily laboratory workup. Since autoimmune hepatitis was included in our differential diagnosis, autoimmune serological testing was conducted. Liver-related autoantibodies tests, including antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA), liver kidney microsome type-1 (LKM-1), and Igg4, came back negative. The hepatitis viral profile (i.e., HAV, HBV, HCV, HEV) was negative. Various additional aetiologies of hepatitis were evaluated and consequently excluded. Serological testing for West Nile virus, Coxsackie virus, Coxiella burnetii, Cytomegalovirus, Echovirus, Leptospira, Measles virus, Varicella Zoster virus, Adenovirus, Epstein-Bar virus was negative. Knowing that dysregulation of hepatic biochemistry is frequent in individuals with rheumatic disorders, an extended rheumatologic panel was performed. The workup included RF, ANA, CCP, dsDNA, pANCA, cANCA, C3, C4, IgG, IgM, ENA, Ro, La, Scl70, and RNP, with final results being normal. Serum protein electrophoresis results revealed hypoalbuminemia. More hepatological studies were conducted since liver function tests continued to be abnormal. Even though a drug-induced liver injury was suspected, a CT-guided liver biopsy was required to confirm the diagnosis and rule out other causes. A liver biopsy was performed, which revealed mild-to-moderate peri-portal inflammation with infiltration from lymphocytes, neutrophils, eosinophils, and mild cholestasis. (Figure. 1a & 1b)

Further evaluation and treatment guidance were requested from a hepatologist due to the gradual progression of cholestatic enzymes. Upon his recommendations, ursodeoxycholic acid (UDCA) was initiated at a dose of 10 mg/kg three times a day for two weeks. Symptoms and lab tests showed a significant and gradual improvement after two weeks of concurrent administration of ursodeoxycholic acid and corticosteroids.

On the nineteenth day of hospitalisation, the patient experienced an episode of shivering while remaining afebrile. Peripheral blood cultures were obtained. Two days later, the results of blood cultures came back positive for Klepsiella pneumoniae and Serratia marcenscens. Based on the antibiogram, intravenous meropenem (2,000 mg every eight hours) was immediately started. Shortly after the seventh day of meropenem treatment, a progressive decrease in platelet count was noticed. There was no ecchymosis, peripheral lymphadenopathy, or petechia in the patient. Since the patient never received heparin, the diagnosis of HIT was ruled out along with DIC subsequently to normal coagulation profile. The differential diagnosis at that time included an upcoming sepsis, haematologic malignancy, immune thrombocytopenic purpura, drug-induced antibodies, bone marrow failure, and an impending infection. The patient failed to maintain a stable platelet count despite having discontinued any potential offending agent, having completed the meropenem 5 days ago, and being on corticosteroids. The platelet count had stabilised at $60x10^3mm^3$. Haematologists were consulted for the thrombocytopenia, and they suspected of drug-induced immune thrombocytopenia (DITP) associated with the antibiotic therapy or an impending sepsis. Since DITP was the most probable diagnosis, intravenous immunoglobulin (IVIG) in a dose of 35 g daily for 5 days was started along with a low dose of methylprednisolone (16 mg S: 1x1;

after several days of dose tapering). An increase in the platelet count (PLT=82 $x10^3mm^3$) was seen on the third day of IVIG therapy and peaked on the fifth day (PLT=100 $x10^3mm^3$). Platelet transfusion was not required. Over four weeks of hospitalisation, he was discharged, having his symptoms significantly subsided and his lab results, particularly the liver enzymes and platelet count, improved after receiving a four-week course of corticosteroid treatment and two weeks of UCDA.

Discussion

Amoxicillin-clavulanate was initially made available for purchase in 1984, then the Netherlands reported the first case of severe hepatitis linked to amoxicillin-clavulanate. (Herrero-Herrero J. G.-A., 2010) In developed societies, DILI is the cause of up to fifty percent of instances of acute liver damage, 10% of all cases of acute hepatitis, and half of people with newly diagnosed jaundice. (Appiah, 15(1), e33445. https://doi.org/10.7759/cureus.33445)

The initial therapeutic approach of DILI involves the immediate discontinuation of the offending drug and supportive measures. (Ferreira I, 2020), (Al-Nabolsi, et al., 2024) Despite the lack of evidence to support their use, supportive management with n-acetylcysteine (NAC) and ursodiol is included in the therapeutic approach. (Al-Nabolsi, et al., 2024) When it comes to DILI, the only widely acceptable treatment is N-acetylcysteine for acetaminophen intoxication. (Giannattasio, 2006) Furthermore, cholestatic manifestations can be highly restrictive and necessitate intervention with antiemetic and analgesic medications, along with cholestyramine, antihistamines, ursodeoxycholic acid, or sertraline to manage pruritus, contingent upon its severity. (Ferreira I, 2020) Al-Nabolsi et al. showed significant improvement of cholestatic symptoms and bilirubin levels following therapy with ursodiol in a case of DILI secondary to amoxicillin-clavulanate. (Al-Nabolsi, et al., 2024) Additionally, a severe case of amoxicillin-clavulanate-related cholestasic hepatitis was reported by José-Ignacio Herrero-Herrero et al. in 2010. The results revealed that treatment with prednisone and ursodeoxycholic acid significantly improved the patient's laboratory results (i.e., total serum bilirubin) and symptomatology, such as jaundice. (Herrero-Herrero J. G.-A., 2010) Additionally, according to the findings of an experimental study, UDCA may be clinically useful in lowering the hepatotoxic side effects of Co-amoxyclav by having a hepatoprotective effect on liver dysfunction brought on by the latest. This effect is ascribed to UDCA's antioxidant qualities. (Gamal A. El-Sherbiny, 2009) According to certain research, two-thirds of drug-induced cholestasis instances were controlled by ursodeoxycholic acid. (Giannattasio, 2006) The detection of eosinophilic infiltrates in liver biopsy specimens, coupled with hypersensitivity symptoms in certain cholestasic individuals, indicate an immunoallergic pathogenesis. Therefore, corticosteroid therapy needs to be considered in patients with serious cholestasic hepatic damage. (Herrero-Herrero J. G.-A., 2010) Giannattasio et al. reported a serious case of cholestatic liver injury due to concurrent treatment with nimesulide and clarithromycin that was effectively controlled with a 2-month course of corticosteroids. However, according to the study's outcomes, treatment with ursodeoxycholic acid for symptoms amelioration (i.e., jaundice, pruritus, and hypertransaminemia) did not yield any benefits. (Giannattasio, 2006)

Concerning our case, it was revealed that the concomitant administration of corticosteroids and ursodeoxycholic acid had substantial improvement in our patient's symptomatology and lab tests. UDCA was administered at a starting dose of 10 mg/kg three times daily, consistent with the recommendations for cholestatic liver diseases.

Based on literature, there are particular criteria in which DILI needs to be strongly considered as a possible diagnosis, including:

(a) the initiation of new medication during the last three months; (b) the existence of rash or eosinophilia; (c) mixed-type (i.e., hepatocellular and cholestatic) hepatic damage; (d) cholestasis with normal hepatobiliary imaging; and (e) acute or chronic hepatitis in the absence of autoantibodies or hypergammaglobulinemia. Even though DILI is unlikely to be ruled out in individuals with any sort of liver injury who do not fit these criteria, its assessment could result in a timely recognition of DILI. (Kazuto Tajiri, 2008) Serological testing or imaging studies should be carried out in order to rule out other possible causes, such as viral infection, autoimmune liver disease, or biliary illness. (Kazuto Tajiri, 2008)

In our case, after ruling out other potential causes of DILI, the initial antibiotic therapy for the peritonsillar abscess was deemed the most likely cause. Several other factors were counted to further support this theory. Firstly, there was a time-related association between the onset of symptoms and the use of antibiotic therapy. Specifically, symptoms of jaundice and pruritus appeared ten days following the initiation of antibiotics. A mixed-type of hepatotoxicity was identified in our case. The liver biopsy results indicated drug-induced liver injury without evidence of liver disease. Furthermore, in our case, drug-induced immune thrombocytopenia was established, even though an in vitro test that could have yielded additional corroborated data regarding the detection of drug-dependent platelet autoantibodies was not available to us. Consequently, to make the diagnosis, we placed a greater emphasis on the clinical picture and laboratory results. IVIG therapy was started in our case since often there is no clear distinction between DITP and ITP. A significant response in platelet count was observed following IVG administration.

DILI is challenging to identify because of its distinct laboratory, clinical, and histopathological characteristics; thus, it still considers a diagnosis of exclusion. (Wettasinghe I., 2023) Currently, there are no standard therapeutic approaches available. (Moole, 2015)

Conclusion: Drug-induced liver injury (DILI) is a rare diagnosis and is still considered a concern in clinical practice. With considerable variation in the latency and pattern of hepatic damage, drug-induced liver injury (DILI) is an unusual but possibly lethal adverse reaction. There is still not a conclusive connection between medications, risk factors, and DILI causes, even though several factors have been suggested. A comprehensive clinical history of associated risks and timeframes, strong clinical evidence, and in-depth hepatological testing are the cornerstones of current best management. The purpose of this case report is to increase awareness of the rare but difficult-to-diagnose side effects of commonly prescribed drugs. By disseminating this knowledge, healthcare providers could be better identified and managed for the potential side effects of prescribed medications.

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