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Case Report

Beyond the Hue: A Peculiar Case of Hyperbilirubinemia

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Abstract

Background: Hyperbilirubinemia can be caused by bile ducts obstruction or by several intrahepatic diseases including genetic disorders. Post-contrast hyperbilirubinemia has been reported in the literature, even though only few cases.

Case Presentation: A 51-year-old woman presented with abdominal pain, jaundice, and generalized itching for seven days. Liver function tests revealed elevated total bilirubin (TBIL 6.7 mg/dL), AST (41 U/L), ALT (117 U/L), and GGT (322 U/L). Contrast enhanced-CT imaging indicated enlarged, fatty liver with common bile duct thickening. Despite initial management, bilirubin levels progressively increased following contrast exposure. MRCP confirmed choledocholithiasis, but ERCP-cholangiography showed no gallstones. Due to the worsening of jaundice a liver biopsy was performed indicating diffuse acute intrahepatic cholestasis. At this point alcoholic hepatitis, acute non-alcoholic hepatits or ischemic hepatitis had been also excluded. Genetic testing was performed revealing a homozygous polymorphism in the UGT1A1 gene, consistent with Gilbert Syndrome. Ursodeoxycholic acid (UDCA) was started (ex-juvantibus approach) and in the following days a reduction in bilirubin levels and symptom improvement was noticed. The patient was subsequently discharged with significant clinical and biochemical improvements.

Conclusion: This case illustrated the diagnostic complexity of prolonged hyperbilirubinemia following contrast agent exposure and the importance of considering genetic predispositions when dealing with drug induced liver injury. Further research is needed in order to understand the mechanism and risk factors associated with contrast induced liver injury.

Introduction

Jaundice is a condition characterized by elevated levels of bilirubin in the blood. Bilirubin is a byproduct of the breakdown of red blood cells and is processed by the hepatocyte. For this reason, elevated levels of conjugated bilirubin, or direct hyperbilirubinemia, typically indicate an underlying hepatobiliary disorder, such as bile duct obstruction, liver inflammation, or drug induced liver injury (DILI) [1,2]. While common causes include viral hepatitis, gallstones, and liver cirrhosis, also rare causes such adverse reactions to contrast agents have to considered [3,4]. Thorough diagnostic evaluation is essential for identifying the underlying cause and guiding appropriate treatment [2,5].

Moreover, genetic predispositions, such as Gilbert Syndrome, may also play a critical role in bilirubin metabolism. Individuals with Gilbert Syndrome have an inherited deficiency in the enzyme glucuronyl-transferase, leading to recurrent episodes of mild jaundice and elevated bilirubin levels, especially under stress or certain medications. Interestingly this genetic factor can exacerbate hyperbilirubinemia when combined with other insults to the liver [6-8].

Case Report

A 51-year-old woman presented to the Emergency Room with abdominal pain, jaundice, and generalized itching for at least 7 days. Due to itching, the patient was treated with Cetirizine for several days before admission to the hospital. The patient was not taking any other medication; she had no history of jaundice or anemia, alcohol abuse, previous blood transfusion or history of travel abroad. Liver tests at presentations were the following: total bilirubin (TBIL) 6.7 mg/dL (normal range 0.3-1.2mg/dl), AST 41 U/L (normal range 8-34U/l), ALT 117 U/L (normal range 7-49 U/l), GGT 322 U/L (normal range 7-73 U/l), lipase 24 U/L (normal range 6-51 U/l), C-reactive protein (CRP) 0.5 mg/dl (normal range 0-0.5 mg/dl). Abdominal computed tomography (with contrast agent Iopromide-Ultravist 370 mg/mL) revealed an enlarged and fatty liver, with thickening of the common hepatic duct, common bile duct, and cystic duct. The gallbladder exhibited thickened walls with contrast enhancement and bile sludge. The distal common bile duct (CBD) was slightly dilated (7-8mm) with a single millimetric gallstone in the pre-papillary tract.

Once the patient was admitted to the hospital fasting, intravenous hydration and itching treatment with chlorphenamine and oxatomide were started. A Magnetic resonance cholangiopancreatography (MRCP) (performed at admission confirmed choledocholithiasis (5-6mm) with a slightly dilated CBD and thickening of the gallbladder wall with bile sludge and gallstones and antibiotic therapy with Ceftriaxone was started. During the first week, there was a slight clinical improvement in itching, without fever or signs of inflammation (White blood cells (WBC) and CRP remained normal). However, liver blood tests showed a progressive elevation of TBIL to 9.4 mg/dL, of which 7.0 mg/dL was direct bilirubin (DBIL). Transaminases and cholestasis indices were slightly elevated (AST 34 U/L, ALT 86 U/L, ALP 260 U/L, GGT 194 U/L), with preserved liver synthesis (Pseudocholinesterase 10142 U/L, INR 0.95, albumin 3.4 g/dL).

Due to the progressive worsening of itching jaundice, and biochemical alterations (TBIL 24.8 mg/dL on 10/04), and accordingly to the MRCP result (indicating obstructive jaundice), an Endoscopic retrograde cholangiopancreatography (ERCP) was performed after few days. Surprisingly, cholangiography showed no gallstones with only a slightly dilated common bile duct (8 mm). A concomitant brushing of the CBD was performed without any evidence of malignant tumour cells. The next day, MRCP was again performed showing a thin CBD without gallstones but with pancreatic head oedema. Although the patient did not report typical abdominal pain, her lipase levels increased to 1234 U/L, resolving spontaneously in the following days.

At the same time hepatotropic viruses, autoimmune diseases, and other conditions such as iron and copper (metals) metabolism alterations were excluded. Furthermore, absence of other possible obstructive reasons of jaundice had been confirmed by a new MRCP describing only features of chronic lithiasic cholecystitis (wall thickening, gallstones) without intra or extra-hepatic biliary dilatation. At this point we decided to perform Liver biopsy. Histological analysis revealed a generally preserved lobular architecture with mild portal and perisinusoidal fibrosis and focal incomplete septa; moderate portal inflammation with lymphocytes, eosinophilic granulocytes and scattered plasma cells was present, with focal interface necrosis, ductular proliferation and biliary metaplasia of periportal hepatocytes. Liver parenchyma demonstrated diffuse hepatocellular and canalicular cholestasis with mild necro-inflammatory activity and mild neutrophilic and eosinophilic infiltration; focal micro-macrovescicular steatosis (< 5%) was also observed. At this point, having excluded alcoholic hepatitis, acute non-alcoholic hepatitis, or ischemic hepatitis, Ursodeoxycholic acid at 900mg/day was started.

To evaluate any underlying condition that may promote jaundice, Gilbert syndrome was tested. In fact, Mutation Polymorphism analysis of the promoter region of the UGT1A1 gene was performed using allele discrimination in Real-Time PCR (IVD-CE Easy UGT1A1 kit, Diatech). Molecular Result confirmed the detection of homozygous polymorphism.

During hospitalization, the patient developed fever and hemocultures tested positive for meropenem sentitive Acinetobacter baumanii that was successfully treated. It is to be noted that, despite infection biochemical tests results were continuously improving in the following days. A progressive reduction of bilirubin and improvement of jaundice and pruritus were observed until complete resolution of symptoms and the discontinuation of cholestyramine. Before discharge on 24/05, Vibration-controlled transient elastography VCTE showed LS 7 kPa and CAP 268 dB/m, while blood exams showed total bilirubin 3.81 mg7dl (conjugated 2.96), AST 66, ALT 72, GGT 20, ALP 98.

Biochemical evaluations in the outpatient setting, confirmed a reduction in bilirubin and improvement in liver tests (TBIL 1.33mg/dL, conjugated 0.79mg /dl, AST 26U/I, ALT 35U/I, GGT 23 U/I).

Discussion

Drug-induced liver injury (DILI) presentations range from a hepatocellular damage with increased transaminases, to a cholestatic hepatitis with mainly elevated alkaline phosphatase (ALP) and/or bilirubin, or it can present as a mixed type where these features overlap. DILI can be due to an idiosyncratic reaction that occurs after the exposure to a drug linked to an unpredictable reaction [1,2]. In our case the patient presented elevated bilirubin levels with slightly elevated transaminases (ALT 81) and mildly elevated ALP (275). Upon calculation of the R-value of 0.69 was obtained falling into the category of cholestatic injury [9]. Informations about hyperbilirubinemia in this scenario can be

confusing. In fact, a liver damage secondary to cetirizine and cephalosporins [10] have been described even though, according to Livertox, the latter are more likely to induce liver damage compared to cetirizine [11]. In addition, data on patients who showed a worsening of hyperbilirubinemia after contrast exposure are available [3,4,12,13].

Several options can be taken into account, in particular ceftriaxone, in this case administered as cholangitis prophylaxis, can be associated with reversible biliary sludge and pseudolithiasis. Ceftriaxone can also lead to an immunoallergic form of cholestatic hepatitis [14]. Moreover, few cases in the literature have been linked to post ERCP prolonged hyperbilirubinemia and only one case has been linked to enhanced MRCP [15]. Exact mechanism is unknown, but it is speculated that it may happen due to contrast agent or cephuroxime administered as prophylaxis [4].

Our patient had a marked increase in bilirubinaemia five days after enhanced-CT scan and prior to ERCP to treat the obstruction previously described.The patient had no previous history of hyperbilirubinemia and no history of liver disease in the relatives. The increase in hyperbilirubinemia was not associated to infections even though the patient developed later on during the stay in the hospital bacteremia due to acinetobacter baumanii [16]. Serology for hepatitis viruses were negative, other etiologies (autoimmune, alcoholic, Wilson and haemocromatosis) were excluded. No signs of haemolysis were present. A liver biopsy revealed marked intrahepatic cholestasis.

Given that, we hypothesized that a genetic bilirubinaemia disorder could be involved in promoting this clinical presentation. Qian et al. described a case of a patient with Gilbert Syndrome who developed post-ERCP hyperbilirubinemia after exposure to the same contrast agent (iopromide) used in the CT scan performed at the Emergency room with worsening levels of bilirubin after enhanced MRCP [15]. Gilbert syndrome is an inherited metabolic disorder characterized by an abnormality in the function of the hepatic enzyme glucuronyl-transferase, which is responsible for bilirubin metabolism. This condition is associated with recurrent episodes of hyperbilirubinemia despite the absence of structural liver diseases or other evident causes of jaundice. It is one of the most common forms of hereditary jaundice, with a prevalence estimated at 2-10% in the general population [17].

Among these conditions, benign recurrent intrahepatic cholestasis (BRIC) is a rare genetic disease characterized by episodes of cholestasis that last from weeks to years, the course is usually benign even though cases of progression from BRIC to progressive familial intrahepatic cholestasis (PFIC) have been described in the literature [18]. Trigger factors include infection, hormonal changes (pregnancy and oral contraceptive pills) and drugs [19,20]. Given the history of the patient (age of the patient and the two previous pregnancies) and the prevalence of the disease we deemed unlikely for the patient to have BRIC and decided to test for UGT1A1 polymorphisms, confirming the homozygous presence of the polymorphism [8].

At present data on contrast agent metabolism and Gilbert syndrome are scarcely available, but it is possible that this disorder may exacerbate the reaction to a cholestatic liver damage [15].

Patients with Gilbert syndrome may experience intermittent jaundice, typically occurring after prolonged fasting, drugs, physical stress, or intercurrent illnesses. However, the condition is generally benign and does not lead to permanent liver damage [6]. Some drugs may selectively affect hepatic bilirubin metabolism as they undergo glucuronidation by UGT1A1. However, the list of drugs and other compounds that affect UGT1A1 activity is much longer, and this UGT1A1 inhibitory activity should be considered in the clinical setting [7].

In this respect, the European Medicines Agency and US Food and Drug Administration now recommend studying the inhibition of UGT1A1 when testing new drugs [21].

To our knowledge, this is the first case of jaundice post intravenous iodinated contrast agent administration by enhanced CT scan but not post exposure during ERCP.

Based on the available data we opted to therapy with UDCA as it is the most common therapeutic option for cholestatic DILI [22]. Alternatively, corticosteroids can be used even though they are more commonly prescribed in hepatocellular injury [23]. In our case bilirubin levels quickly dropped after the introduction of UDCA so no additional treatment was needed.

The case suggested that also contrast agents have to be taken into account among other several drugs in case of prolonged jaundice despite resolution of biliary obstruction. Radiological and sierological findings as well as hystological features ruled out several causes of jaundice.

DILI remains a diagnosis of exclusion and has to be always considered and, among possible trigger of liver damage, also contrast agent.

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References

1. Lu L, Chinese Society of Hepatology and Chinese Medical Association (2022) Guidelines for the Management of Cholestatic Liver Diseases (2021). J Clin Transl Hepatol 10(4): 757: 769.
2. European Association for the Study of the Liver (2009) EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 51(2): 237-267.
3. Patani O, Foulkes SL, Njie R, Aspinall RJ (2010) Prolonged cholestasis induced by endoscopic retrograde cholangiopancreatography. Frontline Gastroenterol 1(2): 121-124.
4. Lin CK, Huang WC (2020) Prolonged cholestasis following endoscopic retrograde cholangiopancreatography, a rare complication of contrast agent induced liver injury: A case report and literature review. Medicine 99(3): 18855.
5. Sullivan JI, Rockey DC (2017) Diagnosis and evaluation of hyperbilirubinemia. Curr Opin Gastroenterol 33(3): 164-170.
6. Vítek L, Tiribelli C (2023) Gilbert's syndrome revisited. J Hepatol 79(4): 1049-1055.

7. Strassburg CP (2008) Pharmacogenetics of Gilbert's syndrome. Pharmacogenomics 9(6): 703-715.
8. Sticova E, Jirsa M, Pawłowska J (2018) New Insights in Genetic Cholestasis: From Molecular Mechanisms to Clinical Implications. Can J Gastroenterol Hepatol 2018: 2313675.
9. Andrade RJ (2019) EASL Clinical Practice Guidelines: Drug-induced liver injury q. J Hepatol 70(6): 1222-1261.
10. (2021) Cephalosporins LiverTox: Clinical and Research Information on Drug-Induced Liver Injury.
11. (2017) Cetirizine. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury.
12. Lee HM, Bonis PAL, Kaplan MM (2006) Persistent cholestatic jaundice after ERCP. Am J Gastroenterol 101(1): 204-205.
13. Musa A Al Ali (2012) Worsening Cholestasis after Endoscopic Retrograde Cholangiopancreatography. J Med J 46(1):65- 68.
14. Ammann R, Neftel K, Hardmeier T, Reinhardt M (1982) Cephalosporin-induced cholestatic jaundice. Lancet 2: 336-337.
15. Qian JD, Hou FQ, Wang TL, Shao C, Wang GQ (2018) Gilbert syndrome combined with prolonged jaundice caused by contrast agent: Case report. World J Gastroenterol 24(13): 1486-1490.
16. Chand N, Sanyal AJ (2007) Sepsis-induced cholestasis. Hepatology 45(1): 230-241.
17. King D, Armstrong MJ (2019) Overview of Gilbert's syndrome. Drug Ther Bull 57: 27-31.
18. Van Ooteghem NAM, Klomp LWJ, Van Berge-Henegouwen GP, Houwen RHJ (2022) Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum. J Hepatol 36(3): 439-443.
19. Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ (2019) Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol 43: 20-36.
20. Nayagam JS, Miquel R, Thompson RJ, Joshi D (2024) Genetic cholestasis in children and adults. J Hepatol 80: 670-672.
21. (2012) Medicines Agency, E. Guideline on the investigation of drug interactions.
22. Björnsson ES (2021) Clinical management of patients with drug-induced liver injury (DILI). United European Gastroenterol J 9(7): 781-786.
23. Saritas U, Aydin B, Ustundag Y (2007) Plasmapheresis and corticosteroid treatment for persistent jaundice after successful drainage of common bile duct stones by endoscopic retrograde cholangiography. World Journal of Gastroenterology: WJG 13(30): 4152-4153.