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CLOPIDOGREL–INDUCED CHOLESTASIS: A CASE REPORT AND REVIEW OF THE LITERATURE.

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ABSTRACT

Clopidogrel is a highly effective antiplatelet agent and is widely used in atherosclerotic vascular diseases especially after cardiac catheterization and percutaneous coronary intervention. Although it appears to be very safe, it may be associated with hepatotoxicity. A 74-year-old male was admitted with anorexia and jaundice. His previous history was significant for hypertension, dyslipidemia, and ischemic heart disease. He had had percutaneous coronary intervention five months previously after presenting with non-ST-elevation myocardial infarction and since then was on dual antiplatelet agents including clopidogrel and aspirin. His other medications included valsartan, atorvastatin, and metoprolol. He was icteric without other positive findings on clinical examination. Extensive investigations suggested cholestasis due to clopidogrel after excluding other causes. Laboratory tests revealed total bilirubin 373.6 µmol/L; direct bilirubin 334 µmol/L; alanine aminotransferase (ALT) 91 IU/L; aspartate aminotransferase (AST) 83 IU/L; alkaline phosphatase (ALP) 978 IU/L, and gamma glutamyl-transferase (GGT) 454 IU/L. The liver profile was normal 5 months earlier. A liver biopsy confirmed pure cholestatic picture. While the patient was waiting for a liver biopsy, his antiplatelet medications were put on hold leading to improvement in cholestasis. Resumption of the clopidogrel after liver biopsy again led to worsening of the cholestasis. On discontinuation of the clopidogrel, jaundice and liver function tests recovered completely within 10 days. Liver function test remained normal on a follow-up review 2 months after the patient was discharged, despite resuming the high-intensity statin dose. Clopidogrel-induced hepatotoxicity is a rare but serious side effect. With increasing use of clopidogrel, all physicians prescribing this medication need to be aware of its' potential to cause hepatotoxicity including cholestasis. The hepatotoxicity associated with clopidogrel is reversible on early discontinuation of this medication.

KEYWORDS: *Clopidogrel, Drug-induced liver injury, hepatotoxicity, cholestasis.*

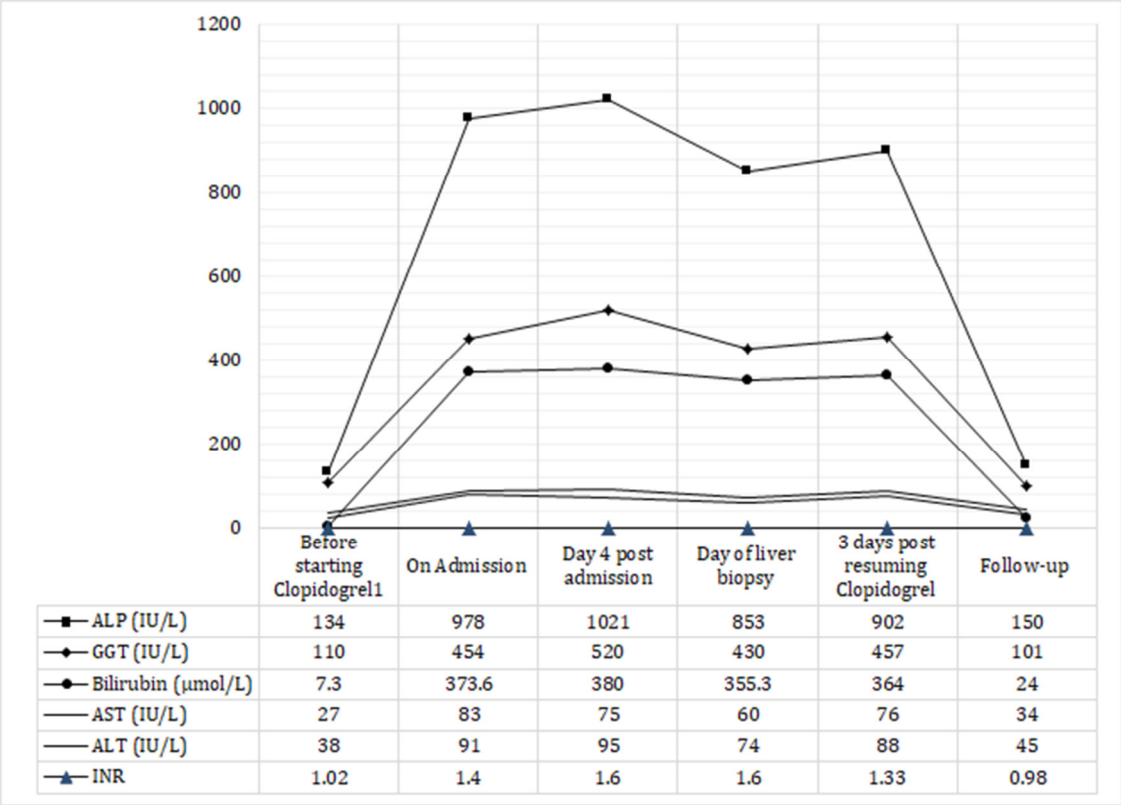
INTRODUCTION

The liver plays an indispensable role in the degradation and excretion of metabolic end-products of many drugs making it at a greater risk for chemical-induced injury.[1] Epidemiologic data suggest that almost one out of 1000 individuals is affected by drug induced liver injury (DILI).[2-3] A wide spectrum of clinical presentations may be seen in DILI and range from asymptomatic mild biochemical abnormalities to acute hepatic failure.[4] Clopidogrel is an oral antiplatelet agent from thienopyridine-class indicated for inhibition of clot formation in peripheral vascular disease, coronary artery disease, cerebrovascular disease, and prevention of myocardial infarction.[5] The use of clopidogrel for the acute coronary syndrome and post-primary percutaneous coronary intervention (PCI) has proved to decrease morbidity and mortality and very effective in protection from recurrent myocardial infarctions.[6-8] Clopidogrel is generally considered a safe drug as it induces minimal side-effects, if any. However, rare and idiosyncratic reactions to clopidogrel such as hepatotoxicity may occur. Except for one case of cholestasis, other reported cases of clopidogrel-induced hepatotoxicity have mainly included a hepatocellular or mixed picture. Only a few of these cases had a rechallenge test, and biopsy proven cases are scarce.[9-26] We report the first case of biopsy-proven and a rechallenge-tested case of clopidogrel-induced hepatic toxicity from Saudi

Arabia. This is only the second case of clopidogrel-induced pure liver cholestasis in the literature. In addition, we present an updated review of clopidogrel-induced hepatotoxicity.

CASE REPORT

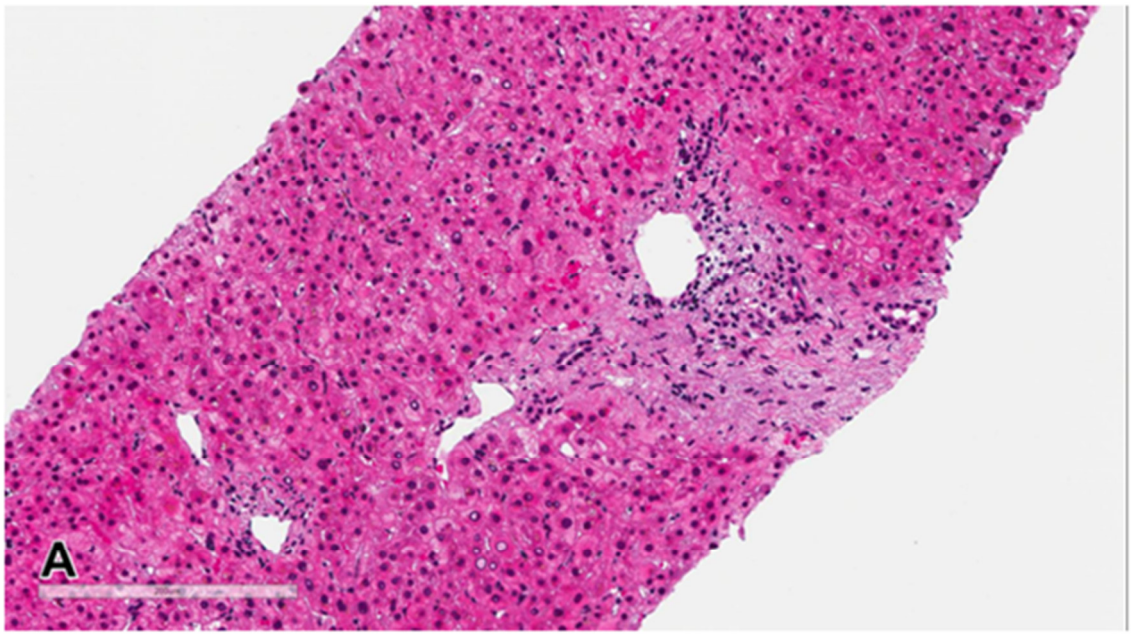
A 74-year-old Saudi male was admitted to a tertiary care hospital in Riyadh, Saudi Arabia with complaints of decreased oral intake and jaundice for 4 months. There was no history of fever, malaise, abdominal pain, weight loss, vomiting, diarrhea, constipation, itching, or change in urine or stool color. There was no history of bleeding from any site. His past medical history was significant for hypertension, dyslipidemia and ischemic heart disease. His medications consisted of aspirin 81mg, atorvastatin 20 mg, furosemide 20 mg, valsartan 80 mg (each once daily), and metoprolol 25 mg twice daily. These drugs were used since his diagnosis of acute coronary syndrome four years ago. He had undergone primary percutaneous coronary intervention (PCI) with drug-eluting stent 5 months ago after a presentation with non-ST-elevation myocardial infarction (NSTEMI). Since then he was started on clopidogrel. He denied use of over the counter, herbal, or illicit drugs and had never smoked or used alcohol. On physical examination, he had deep icterus but was not pale or toxic. Vital signs were unremarkable and there were no stigmata of chronic liver disease. The abdomen was soft with no ascites or organomegaly. Examination of chest, cardiovascular, and neurological system was unremarkable. Laboratory tests (given as test result with normal values in parentheses) revealed elevated level of: total bilirubin 373.6 µmol/L (0–17 µmol/L); direct bilirubin 334 µmol/L (0–7 µmol/L); alanine aminotransferase (ALT) at 91 IU/L (10–55 IU/L); aspartate aminotransferase (AST) 83 IU/L (10–40IU/L); alkaline phosphatase (ALP) 978 IU/L (45–115 IU/L), and gamma glutamyl-transferase (GGT) 454 IU/L (8–61 IU/L). Liver profile was normal 5 months earlier (Figure 1). Renal profile, serum albumin and blood coagulation profile were normal. Serological tests for hepatitis A, B, C, and E were negative. Anti-nuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-smooth muscles antibodies (ASMA), and anti-liver-kidney microsome (LKM) antibodies were negative. His total immunoglobulin (IgG, IgA, and IgM) levels were normal. Tumor markers, carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9, were also negative. Transabdominal ultrasound (US), computerized tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) showed no dilatation of the biliary system excluding any liver or pancreatic masses. In the absence of any mechanical obstruction or other obvious causes of hepatic injury, a cholestatic pattern of DILI was suspected. At the time of admission, the most hepatotoxic of his medications, atorvastatin, was put on hold. However, the liver function tests did not show any improvement. In consultation with cardiology services, clopidogrel was put on hold to do a liver biopsy. While the patient was waiting for the scheduled liver biopsy, liver function tests showed some improvement (Figure 1). A liver biopsy, performed on the day 14 of admission, showed a cholestatic picture with scanty lymphocytes in the portal tracts, without any remarkable interface or lobular inflammation (Figure 2:A and B). The overall picture was suggestive of DILI.



	Before starting Clopidogrel1	On Admission	Day 4 post admission	Day of liver biopsy	3 days post resuming Clopidogrel	Follow-up
ALP (IU/L)	134	978	1021	853	902	150
GGT (IU/L)	110	454	520	430	457	101
Bilirubin (µmol/L)	7.3	373.6	380	355.3	364	24
AST (IU/L)	27	83	75	60	76	34
ALT (IU/L)	38	91	95	74	88	45
INR	1.02	1.4	1.6	1.6	1.33	0.98

Note: Statin was put on hold on admission, liver biopsy taken on day seven after putting clopidogrel on hold, follow-up result two months after discharge from the hospital.

Figure 1
Enzymatic evolution during hospitalization and follow-up



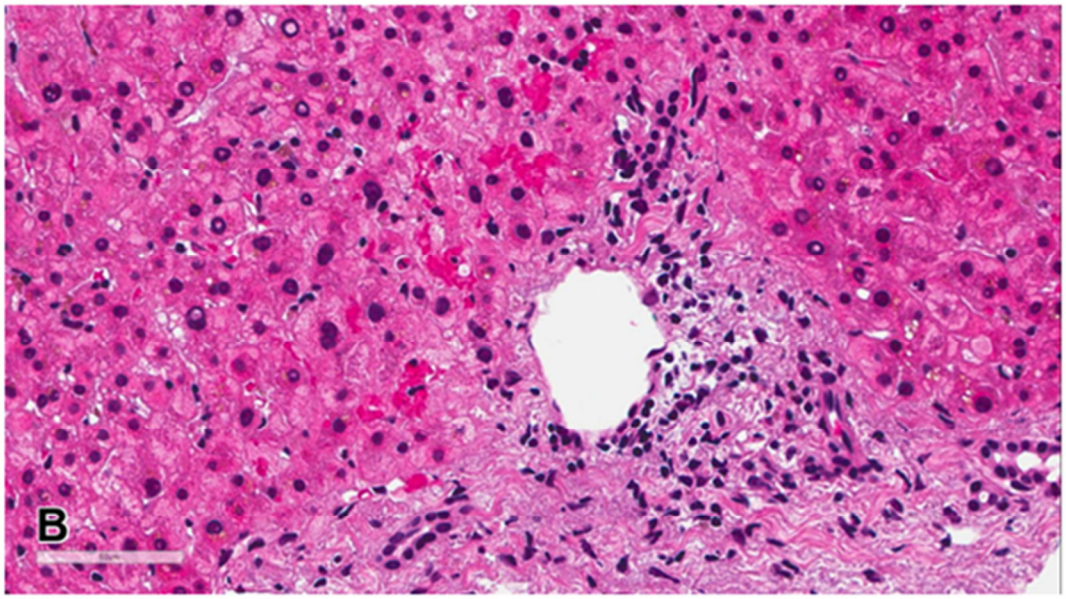


Figure 2
A and B (H&Estain, x20 and x40 respectively) showing cholestatic picture with scanty lymphocytes in the portal tracts, without any remarkable interface or lobular inflammation.

In view of the recent PCI with a drug-eluting stent, the cardiology team strongly recommended resuming the clopidogrel. However, on resuming clopidogrel, the liver enzymes started to rise again. This deterioration of the liver parameter on re-challenge with clopidogrel was considered to be a strong evidence for clopidogrel-induced cholestasis. On discontinuation of the clopidogrel, jaundice and liver function tests recovered completely within 10 days. Liver function tests remained normal on a follow- up review 2 months after the patient was discharged (See Figure 1), despite resuming the high-intensity statin dose.

DISCUSSION

Clopidogrel is a very effective antiplatelet drug with minimal side effects. Main side effects include rashes, indigestion, bleeding, vomiting, and diarrhea.[27] The report on the present case documents the rare but a serious clopidogrel hepatic side effect, cholestasis, the second such report in the literature. On Maria and Victorino diagnostic scale of hepatotoxicity [28] this patient scored 14 out of 20. This was based on a score of 6 for temporal relationship between drug intake and onset of clinical picture, a score of 3 on exclusion of alternative causes, a score of 0 on extrahepatic manifestations, a score of 3 on positive re-challenge test, and a score of 2 on previous case reports of hepatic injury with clopidogrel. This established a probable diagnostic relationship between clopidogrel and hepatotoxicity in our patient. With increasing use of clopidogrel in recent years, the reports of clopidogrel-induced hepatotoxicity are also increasing[29-30]. As of this writing, 18 cases of clopidogrel-induced hepatotoxicity have been reported in the literature[9-26].(Table 1). The case of the present study represents the 19th such report.

Table 1
Reported Cases of Clopidogrel-Induced Liver Toxicity

Reference	Age, Gender	Days at onset	Liver injury pattern	Histology	Outcome
Willens et al (2000)[9]	81, F	21	Mixed	ND	Recovered
Duran Quintana et al (2002)[10]	77, M	180	Mixed	ND	Recovered
Ramos Ramos et al (2003)[11]	89, M	60	Mixed	ND	Recovered
Batwaet al (2003)[12]	57, F	3	Hepatocellular	ND	Recovered
Beltran-Robles et al (2004)[13]	59, M	4	Hepatocellular	ND	Recovered
Chau et at (2005)[14]	74, M	37	Mixed	ND	Recovered
Höllmülleret al (2006)[15]	80, M	43	Mixed	Mixed hepatic and cholestatic	Recovered
Ng et al (2006)[16]	59, F	3	Hepatocellular	ND	Recovered
Lopez-Vincente et al (2007)[17]	63, M	30	Mixed	ND	Recovered
Wiper et al (2008)[18]	56, M	60	Mixed	ND	Recovered
Goyal et al (2009)[19]	78, F	33	Mixed	ND	Recovered
Kastali et al (2010)[20]	63, M	19	Mixed	ND	Died
Monteiro et al (2011)[21]	80, F	30	Hepatocellular	ND	Recovered
Pegram et al (2014)[22]	57, F	3	Hepatocellular	ND	Recovered
Kapila et al (2015)[23]	75, F	5	Hepatocellular	ND	Recovered
Pisapia et al (2015)[24]	53, F	3	Mixed	Hepatocellular and cholestatic	Recovered
Etxeberria-Lekuona et al (2016)[25]	78, M	3	Cholestatic	Cholestatic	Recovered
Keshmiri et al (2016)[26]	34, M	135	Hepatocellular	Hepatocellular	Recovered
Current case	74, M	30	Cholestatic	Cholestatic	Recovered

M= Male, F = Female, ND= Not done

Out of the 19 cases so far reported (including this present case), 8 were females and 11 were males with a mean age of 67.8 years (range 34-89) at the time of the diagnosis. On average, the hepatotoxicity developed 35 days after starting the clopidogrel (range 3-180 days). The majority, 11 of the patients, developed mixed hepatocellular and cholestatic liver injury, 5 patients developed a pure hepatocellular injury, while 2 patients (including the present case) developed a cholestatic picture. Liver biopsy was performed in 5 cases, including the patient of the study, to support the diagnosis.[15,24-26] This patient is the second reported case of biopsy-proven clopidogrel-induced pure cholestatic hepatic injury. Along with clopidogrel, all of these patients were also taking other drugs known to cause hepatotoxicity such as statins, proton pump inhibitors, metoprolol, allopurinol, and valsartan. The majority of the patients survived the clopidogrel-induced hepatotoxicity and improved within one week to 6 months of clopidogrel discontinuation. So far, one fatal outcome has been reported. [20] Although, rechallenge of the patient with the suspected heptotoxic drug is an important component of the Maria and Victorino diagnostic scale of hepatotoxicity,[28] it is often unethical to do so. Our patient was re-exposed to clopidogrel in view of his high risk of thrombosis secondary to PCI with a drug-eluting stent as well as the fact that there had been no previous report of pure cholestatic pathology in the English literature. The exact mechanism of clopidogrel-induced liver injury is unknown. The possible mechanism of clopidogrel-induced liver injury is either direct dose-dependent toxicity or dose-independent idiosyncratic hypersensitivity reaction.[31] Clopidogrel is a prodrug that is oxidized in the liver by several cytochrome P450 (CYP) enzymes including CYP3A4 isoenzyme to an active metabolite carrying a mercapto group.[32] This metabolite is responsible for inhibition of platelet aggregation but also has been shown to be hepatotoxic, possibly through cellular glutathione depletion.[33] This study also suggested that a high CYP3A4 activity was a risk factor for clopidogrel-induced hepatotoxicity, so drugs that induce CYP3A4 such as rifampin could increase the clopidogrel-induced hepatotoxicity. This patient

developed the hepatotoxicity one month after starting clopidogrel and had no hypersensitivity features such as skin rash, arthralgia, and eosinophilia suggesting probably a dose-dependent mechanism of hepatotoxicity. The patient of the present study was also not on any medication known to induce CYP3A4 isoenzyme activity.

CONCLUSION

Clopidogrel-induced hepatotoxicity is a a rare but serious side effect. With increasing use of clopidogrel, all physicians prescribing this medication need to be aware of its' potential to cause hepatotoxicity including cholestasis. The hepatotoxicity associated with clopidogrel is reversible on early discontinuation of this medication.

CONFLICT OF INTEREST

Conflict of interest declared none.

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