Case Report

Clopidogrel-Induced Severe Hepatitis: A Case Report and Literature Review

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Clopidogrel is a commonly prescribed antiplatelet agent that carries a rare risk of hepatotoxicity. We describe a case of severe clopidogrel-induced hepatitis with liver biopsy assessment. Prompt recognition and withdrawal of the offending agent are imperative to prevent progression and potentially fatal liver injury.

1. Introduction

Clopidogrel is a commonly used antiplatelet agent, yet only several cases of hepatotoxicity have been described [1–16]. Liver biopsies were not performed in many of these cases. We report a rare case of severe clopidogrel-induced hepatitis with histological assessment.

2. Case Description

A 34-year-old male with a history of coronary artery disease and remote coronary artery stent was placed on aspirin plus clopidogrel. His baseline liver biochemistries were normal. He had been on clopidogrel for 2 months 12 years ago without adverse effects but discontinued the medication on his own at that time due to nonadherence. Four and a half months after restarting clopidogrel, he presented with jaundice and fatigue. He denied fever, rash, arthralgias, or abdominal pain. His only other medications were aspirin and metoprolol, which he had been on for many years with normal liver biochemistries.

The patient was not on a statin. He denied recent alcohol or herbal medications. Physical examination was significant only for icterus. There was no hepatosplenomegaly, clubbing, rash, asterixis, or other stigmata of chronic liver disease.

Initial bilirubin was 5.7 mg/dL (normal 0.2–1.2 mg/dL), ALT 1,393 U/L (normal 7–48 U/L), AST 1,418 U/L (normal 7–48 U/L), alkaline phosphatase 130 U/L (normal 35–115 U/L), INR 1.5, and partial prothrombin time 37 seconds (normal 15–37 seconds). Extensive serologies were negative to hepatitis A, hepatitis B, hepatitis C (including hepatitis C RNA), hepatitis E, IgM to cytomegalovirus and Epstein-Barr virus, anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, anti-liver kidney microsomal antibody, and ceruloplasmin.

Imaging studies were negative, and bile ducts were not dilated, including by ultrasound, computed tomography, and endoscopic retrograde cholangiopancreatography. No gallstones were present on any imaging modality. Liver biopsy revealed severe acute hepatitis with mixed inflammatory portal tract infiltrates including plasma cells, neutrophils and eosinophils, bile ductular reaction, patchy hepatocyte ballooning degeneration, and extensive periportal hepatocyte dropout, without fibrosis (Figure 1).

The patient was diagnosed with clopidogrel-induced severe hepatitis. Despite discontinuing clopidogrel, AST increased to 2,107 U/L, ALT to 1,567 U/L, and bilirubin to 37 mg/dL (predominately direct bilirubin). INR had increased to 2.1 despite empiric administration of vitamin K. A brief course of prednisone and ursodiol was initiated, with subsequent normalization of liver biochemistries.

3. Discussion

We describe a rare case of severe clopidogrel-induced hepatitis, with histological assessment. Our patient's drug-induced
| Cases                                      | Latency/onset          | Peak ALT (U/L) | Peak bilirubin (mg/dL) | Peak alkaline phosphatase (U/L) | Symptoms                                      | Histology                                      | Outcome          |
|--------------------------------------------|------------------------|----------------|------------------------|-------------------------------|----------------------------------------------|------------------------------------------------|------------------|
| Keshmiri et al. 2016 (current)             | 135 days (4.5 months)  | 1567           | 37                     | 130                           | Jaundice, fatigue                          | Hepatocellular                                   | Recovery         |
| Kapila et al. 2015 [9]                     | 5 days                 | 716            | 1.6                    | 160                           | Nausea, vomiting, fever                     | No liver biopsy                                   | Recovery         |
| Pisapia et al. 2015 [2]                    | 3 days                 | 1603           | 24.5                   | 408                           | Jaundice, arthralgia, papular rash          | Mixed hepatocellular and cholestatic             | Recovery         |
| Monteiro et al. 2011 [13]                  | 30 days                | 540            | 3.5                    | 139                           | Nausea, vomiting                           | No liver biopsy                                   | Recovery         |
| Leighton et al. 2011 [11]                  | 1 day                  | 3626           | 3.3                    | 364                           | Anorexia, jaundice, epigastric pain         | Lymphoplasmacytic portal, interface and lobular hepatitis with no fibrosis | Recovery         |
| Kastalli et al. 2010 [10]                  | 19 days                | 336            | 4.7                    | 186                           | Jaundice, abdominal pain                   | No liver biopsy                                   | Death            |
| Goyal et al. 2009 [3]                      | 23 days                | 1011           | 7.3                    | 1011                          | Abdominal pain, anorexia, jaundice          | No liver biopsy                                   | Recovery         |
| Wiper et al. 2008 [4]                      | 60 days                | 450            | Normal                 | 680                           | General malaise, Abdominal pain, fever      | No liver biopsy                                   | Recovery         |
| López-Vicente et al. 2007 [12]             | 30 days                | 204            | 1.0                    | 682                           | Fever, chills                               | No liver biopsy                                   | Recovery         |
| Ng et al. 2006 [5]                         | 3 days                 | 536            | 1.5                    | 247                           | Weight loss, anorexia, jaundice, nausea, abdominal pain | No liver biopsy                                   | Recovery         |
| Höllmüller et al. 2006 [1]                | 43 days                | 1003           | 20.8                   | 221                           | Mixed hepatocellular and cholestatic        | No liver biopsy                                   | Recovery         |
| Chau et al. 2005 [7]                       | 37 days                | 253            | 6.9                    | 172                           | Jaundice                                    | No liver biopsy                                   | Recovery         |
| Beltran-Robles et al. 2004 [6]             | 4 days                 | 318            | 0.51                   | 100                           | No symptoms mentioned                       | No liver biopsy                                   | Recovery         |
| Wolf et al. 2003 [16]                      | 12 days                | 173            | 1.3                    | 132                           | Fever, leukopenia, weakness                 | No liver biopsy                                   | Recovery         |
| Ramos Ramos et al. 2003 [14]               | 60 days                | 710            | 24.9                   | 118                           | Jaundice                                    | No liver biopsy                                   | Recovery         |
| Duran-Quintana et al. 2002 [8]             | 180 days               | 786            | 13                     | 474                           | Icterus, hepatomegaly                       | No liver biopsy                                   | Recovery         |
| Willens 2000 [15]                          | 21 days                | 507            | 3.0                    | 636                           | Malaise, anorexia, myalgia, icterus         | No liver biopsy                                   | Recovery         |
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Liver biopsy showing severe acute hepatitis with mixed inflammatory portal tract infiltrate (white arrow), patchy hepatocyte ballooning degeneration (black arrow), and extensive periportal hepatocyte dropout (grey arrow).

Liver biopsy showing severe acute hepatitis with mixed inflammatory portal tract infiltrate (white arrow), patchy hepatocyte ballooning degeneration (black arrow), and extensive periportal hepatocyte dropout (grey arrow).

Clopidogrel-induced hepatitis has been described [1–16]. Table 1 lists reported cases in reverse chronological order. The degree of liver injury has ranged from reversible liver injury and recovery [1–9, 11–16] to acute hepatic failure and death [10]. Onset of liver injury in these cases ranges between 3 and 180 days [1–16]. Rechallenge confirmed clopidogrel-induced hepatitis in some of these cases [2–5]. Our patient’s Naranjo scale and RUCAM (Roussel Uclaf Causality Assessment Method) scores were both 8, indicating probable drug-induced hepatitis [17, 18].

Our patient’s liver biopsy revealed severe hepatocellular injury. This adds to the histological findings in clopidogrel-induced hepatitis, as liver biopsy was only performed in 3 of the previously reported cases [1, 2, 11]. Clopidogrel-induced liver injury can be cholestatic, hepatocellular [11], or mixed hepatocellular plus cholestatic [1, 2].

The exact mechanism of clopidogrel-induced hepatitis is unclear. The delayed onset of 4.5 months in our case suggests a toxic-metabolic etiology, whereas the inflammatory infiltrate and response to corticosteroids raise the possibility of a superimposed immune-mediated mechanism of injury. Clopidogrel is a prodrug which is metabolized to inactive clopidogrel carboxylate (90%) and an active metabolite containing a mercapto group (10%) by cytochrome P450 3A4 and 2C19. In vitro studies suggest that the active metabolite is responsible for the hepatotoxicity and that high cytochrome 3A4 activities coupled with cellular glutathione depletion are potential risk factors [19]. Interestingly, an earlier antiplatelet agent, ticlopidine, has also been reported to cause drug-induced cholestatic hepatitis [20, 21].

Clopidogrel-induced hepatitis is a rare but potentially serious adverse effect. A high degree of clinical suspicion is required in patients presenting with abnormal liver biochemistries within a few months after starting clopidogrel. Prompt recognition and discontinuation of the offending agent are necessary, as progressive liver injury and even death can occur.

Competing Interests

The authors declare that they have no competing interests.

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