ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Supriya-Peshin/108

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 2 & Iss: 3

Case Report

To Treat or Not to Treat: A Twist in Paxlovid-Induced Liver Injury Amidst Severe Fatty Liver Disease

Dr. Supriya Peshin*, MD, Dr. Gurvinder Kaur, MD and Dr. Asfand Khattak, MD

Norton Community Hospital, Virginia, USA

Citation: Peshin S, Kaur G , Khattak A. To Treat or Not To Treat: A Twist in Paxlovid-Induced Liver Injury Amidst Severe Fatty Liver Disease. *Medi Clin Case Rep J* 2024;2(3):400-402. DOI: doi.org/10.51219/MCCRJ/Supriya-Peshin/108

Received: 20 July, 2024; **Accepted:** 22 July, 2024; **Published:** 24 July, 2024

***Corresponding author:** Dr. Supriya Peshin, MD, R Norton Community Hospital, Virginia, USA

Introduction

Paxlovid, a combination of nirmatrelvir and ritonavir, has emerged as a critical therapeutic option for the treatment of COVID-19, particularly in high-risk patients. Its efficacy in reducing viral load and preventing severe outcomes has been well-documented, leading to widespread use during the pandemic[1]. However, the drug's interaction profile and potential adverse effects, especially in patients with pre-existing liver or kidney disease, pose significant challenges[2]. Ritonavir, a component of Paxlovid, is a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) enzyme, which can lead to increased plasma levels of co-administered drugs and potential hepatotoxicity[3].

While there is substantial information on Paxlovid's interactions with other medications and its contraindications, the literature on Paxlovid-induced liver injury is relatively sparse. This lack of data is concerning, given the drug's extensive use and the high prevalence of liver disease in the population, including conditions such as non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease. Understanding the risk factors and mechanisms of liver injury in patients taking Paxlovid is crucial for healthcare providers to make informed treatment decisions.

This case report details the clinical course of a 41-year-old male with severe fatty liver disease and a recent history of pancreatitis who developed liver injury following the administration of Paxlovid for mild COVID-19. The case highlights the complexities and potential risks associated with prescribing Paxlovid in patients with pre-existing liver conditions and underscores the need for careful patient selection and monitoring. This report aims to contribute to the growing body of evidence on Paxlovid-induced liver injury and provide insights that may guide clinicians in managing similar cases **(Figure 1)**.

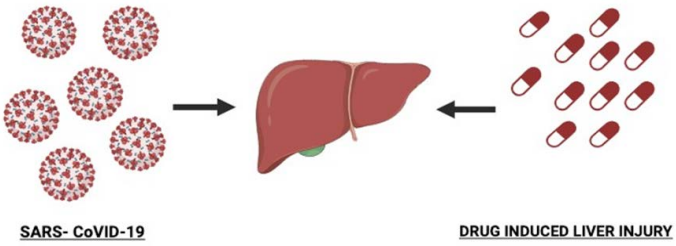

Figure 1: Mechanisms and Manifestations of Liver Injury Induced by Drugs and COVID-19

Case Presentation

History and initial presentation

A 41-year-old male with a significant medical history of severe fatty liver disease, recent pancreatitis, diverticulosis, and gastroesophageal reflux disease (GERD) presented to the emergency department (ED) with complaints of abdominal pain. This pain, which initially was moderate in intensity and radiated to the back, began two weeks prior to his ED visit. During this period, he experienced bouts of nausea and discomfort that progressively worsened.

Upon his initial presentation two weeks earlier, he was diagnosed with severe fatty liver disease and pancreatitis, conditions that were contributing to his abdominal pain and

other symptoms. His treatment at that time included medications to manage nausea and pain, which provided temporary relief. He was advised to follow up with his primary care provider for further management of his fatty liver disease and pancreatitis. Despite these recommendations, his symptoms persisted and worsened over the next week.

Development of liver injury

Approximately one week after the initial episode, the patient contracted a mild case of COVID-19. Given his underlying conditions and the potential for severe outcomes, he was prescribed Paxlovid. After three days of Paxlovid treatment, he began experiencing worsening abdominal pain, leading him to discontinue the medication and seek medical attention at the ED. He reported persistent epigastric pain, a poor appetite, and a general sense of malaise. Notably, he did not identify any specific factors that alleviated or aggravated his pain.

Clinical examination and investigations

Upon evaluation in the ED, the patient's vital signs were as follows:

- **Blood Pressure (BP)**: 136/66 mmHg
- **Heart Rate (HR)**: 98 beats per minute
- **Respiratory Rate (RR)**: 17 breaths per minute
- **Temperature (T)**: 97.6°F

Laboratory results were notable for the following:

- **Sodium (Na)**: 131 mmol/L
- **Potassium (K)**: 4.5 mmol/L
- **Glucose**: 122 mg/dL
- **Blood Urea Nitrogen (BUN)**: 46.0 mg/dL
- **Creatinine (Cr)**: 4.80 mg/dL
- **Alanine Aminotransferase (ALT)**: 48 U/L
- **Aspartate Aminotransferase (AST)**: 90 U/L
- **Alkaline Phosphatase (Alk Phos)**: 907 U/L
- **Lipase**: 160 U/L
- **Total Bilirubin (T-bili)**: 7.8 mg/dL
- **White Blood Cell Count (WBC)**: 16.7 x 10^9/L
- **Hemoglobin (Hgb)**: 13.2 g/dL
- **Platelets (Plt)**: 271 x 10^9/L
- **Lactate**: 1.3 mmol/L

Imaging studies, including a CT scan of the abdomen and pelvis, revealed hepatosplenomegaly and hepatic steatosis. Physical examination findings included right upper quadrant tenderness, jaundice, and abdominal distention. The liver edge was palpable below the costal margin, indicating hepatomegaly.

Hospital Course

The patient was admitted for further evaluation and management. During his hospital stay, he was diagnosed with acute kidney injury (AKI), which was managed effectively with intravenous (IV) fluids, resulting in a prompt and appropriate response. A gallbladder ultrasound was performed, which showed no remarkable findings.

Additionally, a consultation with General Surgery did not reveal any surgical pathology.

Further imaging with magnetic resonance cholangiopancreatography (MRCP) and a hepatobiliary iminodiacetic acid (HIDA) scan revealed intrahepatic biliary stasis, suggesting a cholestatic component to his liver injury. Extensive laboratory workups, including tests for viral hepatitis and autoimmune liver diseases, returned negative results.

Despite ongoing therapy with IV ceftriaxone and metronidazole, his liver function tests (LFTs) continued to rise, indicating a worsening hepatic injury. A Gastroenterology consultation was sought, which suggested that the liver injury was likely drug-induced, attributed to the recent use of Paxlovid. N-acetylcysteine, an antidote for acetaminophen toxicity with potential benefits in other forms of drug-induced liver injury, was recommended and administered.

Over the next three days, the patient's LFTs showed significant improvement, his jaundice resolved, and his abdominal pain subsided. He was discharged in stable condition with a scheduled follow-up appointment with Gastroenterology.

Discussion

This case underscores a potential Paxlovid-induced liver injury in a patient with pre-existing liver disease. While Paxlovid is crucial for managing COVID-19, its use in patients with liver disease necessitates careful consideration. The patient's marked improvement after discontinuing Paxlovid and starting N-acetylcysteine supports the hypothesis of drug-induced liver injury. Given Paxlovid's known interactions and warnings, particularly in those with liver disease, this case emphasizes the need for vigilant monitoring and comprehensive assessment of patient history before prescribing.

Literature Review and Context

Paxlovid, a combination of nirmatrelvir and ritonavir, is primarily metabolized in the liver. Ritonavir, a strong inhibitor of cytochrome P450 3A4 (CYP3A4), can significantly increase the plasma levels of co-administered drugs, potentially leading to hepatotoxicity. Existing literature on Paxlovid-induced liver injury is sparse, but case reports and pharmacovigilance data indicate a possible risk, particularly in individuals with underlying liver conditions.

Conclusion

The prescription of Paxlovid in patients with pre-existing liver disease demands meticulous evaluation due to the potential risk of liver toxicity. This case highlights the importance of balancing the therapeutic benefits of COVID-19 treatment against the risks of exacerbating underlying liver conditions. Healthcare providers should consider alternative treatments and closely monitor liver function when Paxlovid is necessary.

Further research is imperative to elucidate the mechanisms of Paxlovid-induced liver injury and to formulate clearer guidelines for its use in patients with liver disease **(Table 1)**.

Table 1: Adverse effects and mechanisms associated with drug-induced liver and pancreatic injuries.

Type of Injury/Side Effect	Description	**Mechanism**	**References**
Hepatotoxicity	Elevated liver enzymes (ALT, AST), jaundice, hepatic steatosis	Inhibition of CYP3A4 by ritonavir leads to increased plasma levels of co-administered drugs	FDA; NIH
Acute Liver Injury	Sudden onset of liver damage resulting in jaundice, elevated bilirubin, and hepatic failure	Direct hepatotoxic effect and enhanced drug-drug interactions	FDA; NIH; Journal of Hepatology (2020)
Cholestasis	Impairment of bile flow leading to jaundice and elevated alkaline phosphatase	Drug-induced damage to bile ducts or bile transport mechanisms	NIH
Pancreatitis	Inflammation of the pancreas causes abdominal pain, nausea, and elevated lipase/amylase levels	Drug-induced pancreatic injury, possibly through toxic metabolites	FDA
Nause a	Sensation of stomach discomfort and urge to vomit	Gastrointestinal irritation or central nervous system effects	FDA
Diarrhea	Increased frequency of loose or liquid bowel movements	Gastrointestinal irritation and alteration of gut microbiota	FDA
Abdominal Pain	Discomfort or pain in the abdominal region	Gastrointestinal irritation or inflammation	FDA
Vomiting	Forceful expulsion of stomach contents	Gastrointestinal irritation and central nervous system effects	FDA
Hepatic Steatosis	Accumulation of fat in liver cells	Metabolic effects of drug and inhibition of lipid metabolism pathways	NIH
Hyperbilirubinemia	Elevated bilirubin levels cause jaundice	Impairment of bilirubin metabolism and excretion	NIH
Hepatomegaly	Enlarged liver	Chronic liver disease exacerbation due to drug-induced hepatotoxicity	NIH
Gastroesophageal Reflux	Backflow of stomach acid into the esophagus causes heartburn	Gastrointestinal irritation and relaxation of the lower esophageal sphincter	FDA

Monitoring And Management Strategies

The case underscores the importance of vigilant monitoring and comprehensive assessment of patient history before prescribing Paxlovid, especially in individuals with pre-existing liver disease. Key strategies for managing such patients include:

Baseline Liver Function Assessment: Before initiating Paxlovid, a thorough assessment of liver function should be performed, including baseline LFTs and imaging studies if necessary. This helps establish a reference point for monitoring potential drug-induced changes.

Risk-Benefit Analysis: The decision to prescribe Paxlovid should involve a careful risk-benefit analysis, considering the severity of COVID-19, the patient's liver function status, and the availability of alternative treatments.

Close Monitoring: During Paxlovid treatment, patients with liver disease should be closely monitored for signs of hepatotoxicity. Regular LFTs and clinical assessments are essential to detect early signs of liver injury.

Prompt Intervention: If signs of liver injury are detected, prompt discontinuation of Paxlovid and initiation of supportive care, including NAC, should be considered. Early intervention can significantly improve outcomes.

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