

## CASE REPORT

# Fulminant hepatorenal syndrome due to Acetaminophen toxicity: A case report

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## Abstract

HRS is a rare and poor prognosis complication of chronic acetaminophen toxicity, which presents by progressive decline in renal function secondary to liver failure.

## KEYWORDS

acetaminophen, hepatorenal syndrome, metabolic acidosis

## 1 | INTRODUCTION

Hepatorenal syndrome is a rare life-threatening complication of acetaminophen toxicity. It is not responsive to fluid therapy and needs performing an emergent liver transplantation. Here, we introduce a 24-year-old woman with a history of chronic high doses of acetaminophen consumption, presenting with nausea, vomiting, lethargy, oliguria, and severe metabolic acidosis.

Acetaminophen [(N-acetyl-p-aminophenol or APAP), also known as paracetamol, is used for its antipyretic and analgesic properties.<sup>1</sup> It is widely available as single-ingredient or combination formulations with other medications for over-the-counter use which accounts for its high prevalence of toxicity.<sup>2</sup> Although acetaminophen is safely used in therapeutic doses, severe and life-threatening toxicities including renal

injury and acute liver failure (ALF) potentially may occur with doses higher than recommended.<sup>3,4</sup>

Acetaminophen dose-dependent hepatotoxicity is the most frequent cause of ALF (about 50%) in the United States.<sup>5</sup> With doses less than 4 g/d, about 97% of acetaminophen is metabolized by glucuronidation and sulfation to eliminate safely through the kidney.<sup>6</sup> When higher doses of acetaminophen was ingested, its metabolism pathway change to cytochrome P450 system in which acetaminophen metabolized to [N-acetyl-p-benzoquinone imine] (NAPQI), a reactive metabolite leading to irreversible hepatocellular damage.<sup>7,8</sup>

Acute kidney injury (AKI) is another complication of acetaminophen toxicity that happens in less than 2% of cases and may occur either in the presence or in the absence of ALF. While necrosis is responsible for cell death in AKI, it seems that apoptosis is the major cause of hepatocellular

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damage in acetaminophen ALF. ALF-related hepatorenal syndrome (HRS) also may be involved in acute kidney injury (AKI) in acetaminophen overdose.<sup>9,10</sup>

## 2 | CASE PRESENTATION

This study was conducted according to the Declaration of Helsinki principles. Also, CARE guidelines and methodology have been followed in this study. A 24-year-old woman with nausea, vomiting, dizziness, and anorexia was referred to the emergency room (ER) of Imam Khomeini Hospital, Sari, Iran, on December 20, 2020. She had no history of underlying disease. Due to emotional problems, she had been taking 50 to 100 tablets of clonazepam 1 mg and alprazolam 0.5 mg daily for two years. Eight months ago, regardless of the importance of tapering down, she stopped taking these drugs straight off and started to take 50 to 60 tablets of acetaminophen/codeine 300/20 mg and 500 mg daily. Almost from the same time, she gradually became weak and lethargic leading to hospital admission. According to the history of acetaminophen overdose, she consulted a clinical toxicologist.

In the clinical examination, the conjunctiva and skin were pale. The heart rate of 110 beats per minute, blood pressure of 80/50 mm Hg, respiratory rate of 24 per minute, and arterial O<sub>2</sub> saturation of 97% were recorded. On physical examination, the abdomen was soft with tenderness in the right upper quadrant. There was bleeding from the mucosa of the mouth. She was oliguric and underwent urine catheterization. Hydration was started, and a blood sample was sent to the laboratory for routine tests on admission and evaluation of the acetaminophen plasma level. On ultrasound sonography, an increase in the size of the spleen was notable. Space-occupying lesions were not seen in the parenchyma of the liver, spleen, kidneys, and pancreas. Liver echography and bile ducts were normal. No mass and free fluid was visible inside the abdomen. On ECG, sinus tachycardia was detected. Viral markers including HIV, HBsAg, and HCV Ab were negative. ABG showed severe metabolic acidosis. Other laboratory data are in Table 1.

She was immediately transferred from the emergency room to the ICU. She had hematemesis consisting of acetaminophen tablet residues which explained upper gastrointestinal bleeding. Tachypnea and loss of consciousness secondary to the hepatic encephalopathy resulted in intubation. According to the metabolic acidosis and raised creatinine, the three-hour hemodialysis was performed. Treatment was started with N-acetylcysteine (NAC), pantoprazole, norepinephrine, albumin, fresh-frozen plasma, packed cell, vitamin K, magnesium sulfate, and sodium bicarbonate. Dextrose water 50% was also administered to improve her hypoglycemic state.

**TABLE 1** Baseline laboratory data

Hemoglobin	7.9 g/dL
White blood cells	9000/mm <sup>3</sup>
Platelet	142000/mm <sup>3</sup>
Sodium	143 mmol/L
Potassium	3.5 mmol/L
ALT	2030 IU/L
AST	1691 IU/L
ALP	303 IU/L
Bilirubin	
Total	2.3 mg/dL
Direct	0.8 mg/dL
Lactate dehydrogenase	5400 IU/L
PT	39.2 sec
PTT	58 sec
INR	4.8
Albumin	2.5 g/dL
Calcium	7.9 mg/dL
Magnesium	1.6 g/dL
Blood urea nitrogen	16.82 mg/dL
Creatinine	3 mg/dL
pH	7.19 mmHg
HCO <sub>3</sub>	9.6 mmol/L
PCO <sub>2</sub>	24.7 mmHg
Base excess	−18.6 mmol/L
Blood sugar	50 mg/dL

Based on the impaired LFT profile and her coagulopathy, she consulted a gastrointestinal specialist and a surgeon for an urgent liver transplantation. Despite the intensive supportive therapy during the first 24 hours and efforts to correct the metabolic acidosis and electrolyte disorders, no response was detected, and unfortunately, she died.

## 3 | DISCUSSION

Acetaminophen, a safe and effective analgesic, and antipyretic agent can cause irreversible, even fatal damage to the liver and kidney with chronic high-dose consumption. Early presentation and diagnosis of acetaminophen overdose are critical for successful management. Acetaminophen is rapidly absorbed after oral administration with the onset of action 30 minutes to 2 hours. Peak plasma levels reach 4 hours after overdoses, which could prolong in gastrointestinal hypomotility or administration of extended-release formulation.<sup>1,11</sup> In acute situations, during the first 4–6 hours after consumption, oral activated charcoal reduces the gastrointestinal absorption and subsequent acetaminophen plasma level. A free radical scavenger, NAC, is also effective against the

replenishing glutathione stores caused by oxidative metabolite of acetaminophen and could prevent or reduce the severity of acetaminophen hepatotoxicity.<sup>12</sup>

The normal elimination half-life of 2 hours could prolong to 17 hours in severe hepatic dysfunction.<sup>13</sup> It is well known that in acute ingestion of acetaminophen, Rumack-Matthew nomogram is used to make decisions about initiation and to evaluate the treatment trend. This nomogram cannot be used in chronic toxicity to predict the time of treatment initiation due to the lack of correlation between plasma levels and the degree of acetaminophen ingestion. However, treatment is indicated in such patients with concurrent elevated transaminases regardless of acetaminophen plasma level. It has been recommended to treat patients either with acetaminophen plasma levels of more than 20 mcg/mL or with increased transaminases.<sup>1</sup> Accordingly, NAC was started for this case, with acetaminophen plasma level of 84.7 mcg/mL, but it could not be effective based on the extensive liver and kidney oxidative injuries.

Late presentation, like our case, may manifest as a rise in alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin that represents the hepatic phase of acetaminophen toxicity.<sup>14</sup> Actually, this case was on chronic acetaminophen abuse and presented by both liver and kidney dysfunction which did not respond to any treatment options. About this patient, chronic consumption of acetaminophen had led to the impairment of hepatic metabolism pathways; therefore, prolonged half-life of acetaminophen had been caused further hepatic injury.

In overdoses, the acetaminophen metabolic pathway shifted to produce more oxidative NAPQI metabolites that could be excreted in urine. As a result, glutathione stores of the kidney will be reduced and tubular injury occurs.<sup>15</sup>

She also became oliguric with a creatinine level of 3 mg/dl, representing acetaminophen renal injury. Acetaminophen-related renal injury occurs more in chronic users with significant elevation in liver transaminases.<sup>16</sup> There are some situations of concurrent kidney and liver involvements that are necessary to be differentiated from HRS. Regarding no history of fever and blood and ascites cultures; no history of bleeding and NSAIDs consumption; and no history of infections, injection of dye, intake of nephrotoxic agents such as aminoglycosides in this case that are associated with infection, prerenal acute kidney injury, and parenchymal renal disease, respectively, HRS could be considered. Also, it is important to differentiate acute tubular necrosis (ATN) that is the most common type of acetaminophen-induced nephrotoxicity, from HRS.<sup>6</sup> Since the patient did not respond to fluid replacement (that is not common in ATN), and among her liver failure, increased serum creatinine, oliguric state, and lethargy, HRS was considered as a consequence of chronic acetaminophen hepatotoxicity. HRS is described as a progressive reduction in renal function resulting from

severe liver failure, which often happens in cirrhotic patients. HRS has a poor prognosis, particularly in type 1, and its mortality rate is high within 2 weeks unless performing an urgent liver transplantation.<sup>17</sup> This case was also a candidate for liver transplantation but unfortunately died before any preparations.

## 4 | CONCLUSION

It is important to distinguish HRS from ATN, which is the most reported cause of acetaminophen-induced nephrotoxicity, to select a certain treatment strategy. HRS is a rare and poor prognosis complication of chronic acetaminophen toxicity, which presents by progressive decline in renal function secondary to liver failure. The curable treatment option in this situation may be liver transplantation, the same as HRS in cirrhotic patients.

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## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## AUTHOR CONTRIBUTIONS

ZZ: involved in interpretation and collecting of data, and editing the manuscript. MM: involved in drafting first version of manuscript and editing. ZN: involved in writing, editing, and preparing the final version of manuscript. MF: involved in critical revising. RT is responsible for collecting data and submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

## INFORMED CONSENT

Informed consent for the publication was taken from the patient's parents.

## DATA AVAILABILITY STATEMENT

The data are available with the correspondence author and can be gained on request.

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