Rom J Leg Med [31] 71-75 [2023]
DOI: 10.4323/rjlm.2023.71

A RARE CASE OF ACUTE HEPATITIS FOLLOWING PARAQUAT POISONING

Ami Merul Mehta[1], Shankar M Bakkannavar[2,*], Deepak Nayak[3]

[1]Kasturba Medical College, [2]Kasturba Medical College, Department of Forensic Medicine and Toxicology, [3]Kasturba Medical College, Department of Pathology, Manipal, MAHE, Manipal, India

Abstract: *Background.* Despite the high incidence of paraquat poisoning in developing countries such as India, there is limited literature describing its hepatic implications. Thus, this case report aims at bridging the gap in the knowledge of the hepatic effects of paraquat consumption.

Objective. To elucidate a rare case of acute cholestatic hepatitis following paraquat consumption.

Case History. A 65-year-old male, who allegedly consumed pesticide secondary to depression, was brought to local Hospital from where he was shifted to tertiary care teaching hospital in South India for further treatment. He died two days later while under treatment. Postmortem examination revealed diffuse visceral congestion. Internal examination of the gastrointestinal tract revealed congestion of the esophageal mucosa and 30 ml of creamy mucoid fluid with no identifiable food particles and no abnormal perceptible odor in the stomach and proximal small intestine.

Post-mortem toxicologic studies revealed serum creatinine of 1.36 mg/dL, serum sodium of 132 mmol/L, total bilirubin of 1.48 mg/dL and direct bilirubin of 0.50 mg/dL. Urine sample tested positive for paraquat.

The cause of death from perusal of autopsy findings, hospital findings and histopathology report and RFSL report was attributed to complications secondary to the oral consumption of paraquat and the manner of death was certified as suicide (intentional self-harm).

Conclusion. Histopathological studies are paramount in the diagnosis of hepatitis secondary to paraquat consumption. Such an unusual case is one of the first of its kind reported in the Indian scenario, to the best of our knowledge. Further studies are needed to elucidate the mechanisms and types of hepatic injuries caused by paraquat ingestion.

Keywords: forensic autopsy, paraquat poisoning, acute hepatitis.

INTRODUCTION

Self-poisoning with paraquat is not uncommon in developing countries such as India. Studies revealed a very high in-hospital mortality rate of 72.7% [1]. There are limited Indian studies on paraquat poisoning, especially pertaining to hepatic implications.

The high case fatality rate is attributed to the inherent toxicity of paraquat, the lack of well-established guidelines for treatment and the absence of a specific antidote. Mechanisms of toxicity include free radical damage, oxidative stress and its secondary effects such as lipid peroxidation, mitochondrial toxicity, activation of NF-kB and apoptosis. Rough and smooth endoplasmic reticulum degranulation and mitochondrial damage occur in the liver leading to congestion and acute hepatic injury [2].

Limitations in establishing the diagnosis include illiteracy and ignorance of the patients, lack of specific signs and lack of training of medical officers in treating patients with paraquat poisoning [3].

This case report aims at bridging the gap in the knowledge of the hepatic effects of paraquat consumption. Thus, we hope to reduce the long-term effects and mortality associated with paraquat consumption.

CASE HISTORY

A 65-year-old male, who allegedly consumed pesticide secondary to depression, was brought to local Hospital from where he was shifted to tertiary care teaching hospital in South India for further treatment. The patient was apparently asymptomatic till 5:30 pm

*Correspondence to: Shankar M Bakkannavar MD, Associate Professor, Kasturba Medical College, Department of Forensic Medicine and Toxicology, Manipal - 576104, India, E-mail: shankar.mb@manipal.edu

on 9/01/21, after which there was an alleged history of consumption of GRAMOXONE (Paraquat) of 100-150 mL, following which he developed 2-3 episodes of non-bilious, non-blood stained, watery vomiting. He was then taken to a local hospital where he was given a stomach wash and Injection Atropine. There were 4-5 episodes of vomiting following which he was brought to Kasturba Hospital. He was admitted to the ICU for further evaluation and management.

On admission, GCS was 12/15 and vitals were stable. Urine studies revealed 2+ sugar, 3+ protein, 3+ blood and 2+ leucocytes suggestive of acute renal injury. He was started on symptomatic management with N-Acetyl Cysteine (NAC) and IV fluid hydration. At 6:40 am on 10/01/21, the patient sustained a respiratory arrest and became unresponsive, hence the emergency team was called. ROSC was achieved and then the patient was shifted to the higher ICU for further management.

In view of the patient's arrest, he was intubated emergently and put on VCV at 100% flo2. During intubation the patient's BP plummeted and hence he was started on inotropic support (triple inotropes). ABG showed features suggestive of severe metabolic acidosis (pH 6.9 pO2 349.7 PCO2 47.5 HCO3 8.2). For this reason, a nephrology consult was sought and the patient was advised hemoperfusion.

The patient was continued on supportive measures, NAC and solumedrol, and hemoperfusion was started, but five minutes after commencement, the patient developed severe hypotension of 70/50 mm Hg and was started on triple inotropes (Adrenaline, Vasopressin, Noradrenaline). The ECG showed new onset ST depression; hence the procedure was stopped midway in view of his deteriorating condition. The patient's vitals, BP and electrolytes were monitored regularly. His urine output progressively reduced and serial ABGs showed worsening metabolic acidosis and low levels of bicarbonate, hence bicarbonate infusions were given.

Despite all the above measures, the patient sustained a cardiac arrest at 5:25 am on 11/01/21, and could not be revived despite all resuscitative measures and high-quality CPR.

Postmortem examination revealed a 170 cm, 58 kg elderly male with several therapeutic artefacts including pink adhesive bandages over right and left side of neck and right groin with multiple underlying needle puncture marks. Post mortem lividity was present over the back and was not fixed. External orifices appeared normal and there were no other external injuries. Internal examination revealed diffuse visceral congestion. The brain was soft, edematous and congested. The lungs were firm, congested and edematous through which blood-stained fluid oozed out on cut section, with the right lung weighing 935 g and left lung weighing 880 g. Pleura contained 150 mL of straw-colored fluid. Tracheal mucosa was congested. Aorta showed multiple fatty streaks over the intima.

Internal examination of the abdomen and gastrointestinal tract revealed congestion of the esophageal mucosa and 30 mL of creamy mucoid fluid with no identifiable food particles and no abnormal perceptible odor in the stomach. The stomach mucosa was hemorrhagic at several places. The proximal part of the small intestine contained similar contents. The liver weighed 894 g and showed yellowish discoloration and was congested on cut section. The spleen weighed 90 g and was congested on cut section. Kidneys revealed congestion on cut section and the right and left kidneys weighed 120 and 124 g respectively.

Post-mortem toxicologic studies revealed serum creatinine of 1.36 mg/dL, serum sodium of 132 mmol/L, total bilirubin of 1.48 mg/dL and direct bilirubin of 0.50 mg/dL. Urine sample tested positive for paraquat. No other drugs or volatile substances were detected.

A piece of lung, liver and kidney were sent for histopathology examination. In addition, entire stomach and its contents and the proximal 30 cm of small intestine with its contents, 500 g of liver with gall bladder and half of each kidney, and 10 mL of blood were sent to Regional Forensic Science Laboratory (RFSL) in glass bottles for chemical analysis. The colour test and thin layer chromatographic methods of analysis responded for the presence of Paraquat (Herbicide) in the viscera and blood sent. Histopathology examination of the piece of liver suggested acute (cholestatic) hepatitis (Figs 1 and 2).

The cause of death from perusal of autopsy findings, hospital findings and histopathology report and RFSL report was attributed to complications secondary to the oral consumption of paraquat and the manner of death was certified as suicide (intentional self-harm).

DISCUSSION

Paraquat, or N, N'-dimethyl-4,4'-bipyridinium dichloride, also known as methyl viologen, is a herbicide widely used in the Indian subcontinent. Self-poisoning with paraquat is not uncommon in developing countries

such as India.

The high case fatality rate is attributed to both to its inherent toxicity, the lack of well-established guidelines for treatment and the absence of a specific antidote [3].

Clinical manifestations depend on the amount of paraquat ingested. Mild poisoning (less than 20 mg PQ ion per kg body weight (bw) manifests as gastrointestinal symptoms with mild renal damage. Severe poisoning (20–40 mg PQ ion per kg bw) presents in the form of acute renal failure, acute lung injury and advanced pulmonary fibroses, which causes respiratory failure 2–3 weeks after ingestion. Fulminant poisoning (greater than 40 mg PQ ion per kg bw = 20 mL of 20–24% concentrate) leads to multiple organ failure and death in all patients within hours to a few days after the PQ ingestion.

There are a spectrum of clinical manifestations (most commonly gastrointestinal and pulmonary) including nausea, vomiting, aphthous stomatitis, weakness, lethargy, oral canker sores, painful lesions, tongue and throat redness, jaundice, dyspnea, bilateral crackles, crepitation, rales, tachypnea, fever, sialorrhoea, pupil mydriasis, oral and lips burn, body pain, and digestive problems [4]. 'Paraquat tongue' (mucosal ulceration in the oral cavity and tongue) is another common manifestation seen within the first few days of poisoning [5].

It is widely known that the mechanism of injury involves free radical damage. Our case is unique in that it highlights the possible hepatic manifestations of paraquat consumption, which is less commonly studied. Paraquat-induced acute liver injury is attributed to the induction of mitochondrial damage, LPO, and secretion of pro-inflammatory molecules (including iNOS, TNF-α IL-1β). Another mechanism is the depletion of phase I and phase II xenobiotic metabolizing enzymes (including cytochrome P450 (CYP) and GST, GP-X, MPO, and CAT) thus attenuating the ability to withstand oxidative stress. All of the above contribute to an increase in serum AST, ALT, and ALP activities and total bilirubin. Furthermore, recent studies indicate that acute hepatitis, the time taken to arrive at the hospital, and PO2 at admission are powerful predictors of AKI in paraquat-intoxicated patients and thus the mortality associated with the condition [4].

It is to be noted that hepatic pathology following paraquat exposure appears to be associated with concurrent high alcohol intake [6]. Alcohol induced liver damage is partly due to an altered redox potential leading to lipid peroxidation and low glutathione, amplifying the effect of paraquat. It is based on this mechanism that N-acetyl cysteine has been used experimentally in an attempt to mitigate paraquat induced damage following ingestion.

Another interesting attribute to note pertaining to this case is the histopathological liver picture . Studies have shown that in such cases the liver shows foci of hepatocellular necrosis and liver cell dropout together with sinusoidal dilatation and congestion and widening of portal tracts by reticulin deposition [6]. Similar findings were noted in our case.

Although the pathogenesis of liver injury remains unclear, the available evidence indicates that hepatocellular and later bile duct injury play a role. The early recovery of hepatocellular damage attributes to the rarity of liver failure in paraquat poisoning while the severe jaundice could be attributed to the late recovery of bile duct injury, leading to prolonged cholestasis. An experimental study showed that biliary

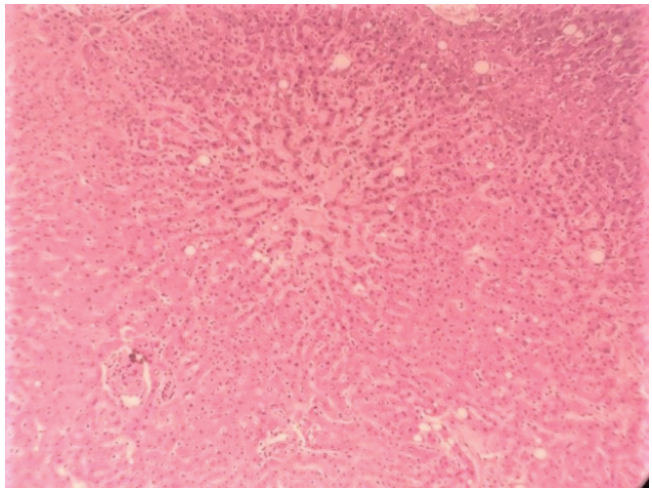

Figure 1. Hepatic lobule showing centrilobular hepatocytes with intracanalicular cholestasis (H&E; x50).

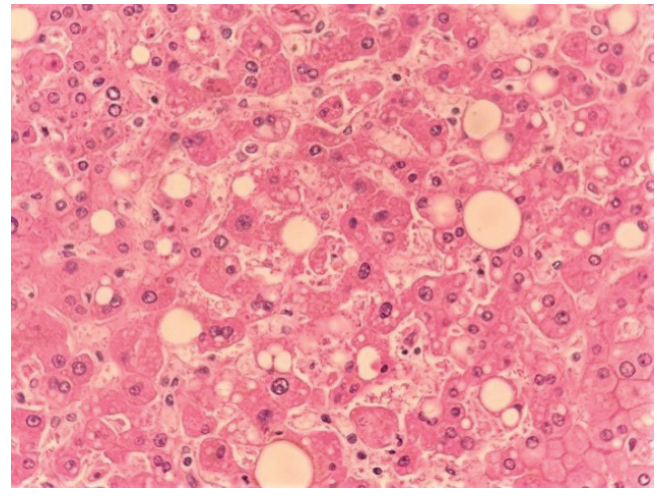

Figure 2. Hepatocytes with intracanalicular cholestasis, steatosis and focal spotty necrosis (H&E; x200).

cells underwent degeneration and necrosis followed by periductal fibrosis surrounding the regenerating bile duct epithelium three weeks later further strengthening evidence suggesting the chronicity of bile duct damage [7]. Hepatitis following paraquat exposure is uncommon, mild and transient, however it is associated with higher incidences of respiratory and renal failure complications [8].

The definitive treatment protocol for such cases is still not well established. Gastrointestinal decontamination using Bentonite (7.5%), Fuller's Earth (15%), or activated charcoal along with possible hemodialysis or hemoperfusion is recommended for patients who present within 2–4 h of ingestion. Oxygen therapy in mild to moderate hypoxia should be avoided as it may worsen the oxidative damage. Antioxidants like vitamin E, vitamin C, N-acetyl cysteine, betanin, salicylic acid, and desferrioxamine B have also shown to have therapeutic benefit in these patients. Similarly, immunosuppressive therapy with glucocorticoids and cyclophosphamide though widely used, have not been substantially studied [9-11].

Recent studies have shown that H2S attenuated the paraquat-induced acute liver injury by enhancing antioxidative capability, regulating mitochondrial function, and suppressing ROS-induced NLRP3 inflammasome activation, thus proving to be a novel therapeutic strategy in such cases [12]. Other novel strategies include edaravone, methylene blue, curcumin, thymoquinone, ellagic acid, Matricaria chamomilla, genistein and Levisticum officinale [13-20].

Further case series of such patients are vital in establishing a definitive strategy for management. PT, PTA, INR, TBil, DBIL, IBIL, ALT, AST, ALT/AST, BUN, and CR were highly correlated to PQ poisoning and showed statistical significance ($p<0.05$) in predicting the prognosis of PQ poisoning and thus may prove to be an efficient method in predicting prognosis in the future [21, 22].

In conclusion, our case describes a rare hepatic manifestation of paraquat consumption and can aid in reducing the morbidity and mortality associated with this condition.

Histopathological studies are paramount in the diagnosis of hepatitis secondary to paraquat consumption. Such an unusual case is one of the first of its kind reported in the Indian scenario, to the best of our knowledge. Further studies are needed to elucidate the mechanisms and types of hepatic injuries caused by paraquat ingestion.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical consideration

The name of the victim and medical officer were not revealed.

References

1. Ravichandran R, Amalnath D, Shaha KK, Srinivas BH. Paraquat Poisoning: A Retrospective Study of 55 Patients From a Tertiary Care Center in Southern India. Indian J Crit Care Med. 2020;24(3):155-159.
2. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72(5):745-757.
3. Dambal A, Naik S, Hemamalini G, Siddaganga S, Kashinkunti MD. Reasons for under-reporting of paraquat poisoning in India. Natl Med J India. 2021;34(3):138-142.
4. Shadnia S, Ebadollahi-Natanzi A, Ahmadzadeh S, Karami-Mohajeri S, Pourshojaei Y, Rahimi HR. Delayed death following paraquat poisoning: three case reports and a literature review. Toxicol Res (Camb). 2018;7(5):745-753.
5. Chandra A, Shah KA, Mahato S, Bhattacharjee MS, Mandal T. Paraquat poisoning. BMJ Case Rep. 2021;14(11):e246585.
6. Moar JJ, Hill L. Histopathological Findings in a Fatal Case of Paraquat Poisoning. Am J Forensic Med Pathol. 2022;43(1):69-72.
7. Muthu V, Das A, Bal A, Agarwal R. Severe cholestasis and hepatic dysfunction in a case of fatal paraquat poisoning. Clin Res Hepatol Gastroenterol. 2015;39(1):e7-9.
8. Yang CJ, Lin JL, Lin-Tan DT, Weng CH, Hsu CW, Lee SY, Lee SH, Chang CM, Lin WR, Yen TH. Spectrum of toxic hepatitis following intentional paraquat ingestion: analysis of 187 cases. Liver Int. 2012;32(9):1400-1406.
9. Firouzian F, Pourshoja P, Nili-Ahmadabadi A, Ranjbar A. Hepatoprotective effect of N-acetylcystein loaded niosomes on liver function in paraquat-induced acute poisoning. Pestic Biochem Physiol. 2019;160:146-153.
10. Han J, Zhang Z, Yang S, Wang J, Yang X, Tan D. Betanin attenuates paraquat-induced liver toxicity through a mitochondrial pathway. Food Chem Toxicol. 2014;70:100-106.
11. Kanchan T, Bakkannavar SM, Acharya PR. Paraquat Poisoning: Analysis of an Uncommon Cause of Fatal Poisoning from Manipal, South India. Toxicol Int. 2015;22(1):30-34.
12. Liu Z, Wang X, Li L, Wei G, Zhao M. Hydrogen Sulfide Protects against Paraquat-Induced Acute Liver Injury in Rats by Regulating Oxidative Stress, Mitochondrial Function, and Inflammation. Oxid Med Cell Longev. 2020;2020:6325378.
13. Yi R, Zhizhou Y, Zhaorui S, Wei Z, Xin C, Shinan N. Retrospective study of clinical features and prognosis of edaravone in the treatment of paraquat poisoning. Medicine (Baltimore). 2019;98(19):e15441.
14. Chen JL, Dai L, Zhang P, Chen W, Cai GS, Qi XW, Hu MZ, Du B, Pang QF. Methylene blue attenuates acute liver injury induced by paraquat in rats. Int Immunopharmacol. 2015;28(1):808-812.
15. Kheiripour N, Plarak A, Heshmati A, Asl SS, Mehri F, Ebadollahi-Natanzi A, Ranjbar A, Hosseini A. Evaluation of the hepatoprotective effects of curcumin and nanocurcumin against paraquat-induced liver injury in rats: Modulation of oxidative stress and Nrf2 pathway. J Biochem Mol Toxicol. 2021;35(5):e22739.
16. Zeinvand-Lorestani H, Nili-Ahmadabadi A, Balak F, Hasanzadeh G, Sabzevari O. Protective role of thymoquinone against paraquat-induced hepatotoxicity in mice. Pestic Biochem Physiol. 2018;148:16-21.

17. Qi M, Wang N, Xiao Y, Deng Y, Zha A, Tan B, Wang J, Yin Y, Liao P. Ellagic acid ameliorates paraquat-induced liver injury associated with improved gut microbial profile. Environ Pollut. 2022;293:118572.
18. Tavakol HS, Farzad K, Fariba M, Abdolkarim C, Hassan G, Seyed-Mostafa HZ, Akram R. Hepatoprotective effect of Matricaria chamomilla.L in paraquat induced rat liver injury. Drug Res (Stuttg). 2015;65(2):61-64.
19. Semeniuk M, Ceré LI, Ciriaci N, Bucci-Muñoz M, Quiroga AD, Luquita MG, Roma S, Catania VA, Mottino AD, Rigalli JP, Ruiz ML. Protective effect of genistein pre-treatment on paraquat hepatotoxicity in rats. Toxicol Appl Pharmacol. 2021;426:115636.
20. Afarnegan H, Shahraki A, Shahraki J. The hepatoprotective effects of aquatic extract of Levisticum officinale against paraquat hepatocyte toxicity. Pak J Pharm Sci. 2017;30(6(Supplementary)):2363-2368.
21. Hu L, Li H, Cai Z, Lin F, Hong G, Chen H, Lu Z. A new machine-learning method to prognosticate paraquat poisoned patients by combining coagulation, liver, and kidney indices. PLoS One. 2017;12(10):e0186427.
22. Zhang S, Song S, Luo X, Liu J, Liu M, Li W, Cao T, Li N, Zeng C, Zhang B, Cai H. Prognostic value of liver and kidney function parameters and their correlation with the ratio of urine-to-plasma paraquat in patients with paraquat poisoning. Basic Clin Pharmacol Toxicol. 2021;128(6):822-830.