Case Report

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Sepsis-Associated Cholestasis: The Impact of Mitochondrial Dysfunction (A Case Report)

Behzad Noroozi[1], Ali Mohammad Hadi[2], Bita Shahrami[1], Ayda Vakili Ardabili[3], Fatemeh Yoonesi[3], Kaveh Hedayati Emami[3], Hamid Reza Sharifnia[3], Mojtaba Mojtahedzadeh[1]

[1] Clinical Pharmacy Department, Tehran University of Medical Sciences, Tehran, Iran

[2] Clinical Pharmacy Department, College of Pharmacy, University of Basra, Basra, Iraq

[3] Anesthesiology and Intensive Care Department, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Introduction: Hyperbilirubinemia – a condition of elevated serum bilirubin above the reference range, is common in hospitalized patients. The reasons for the increase in the bilirubin level can be pre-hepatic, hepatic, and post-hepatic. Sepsis is one of the most important causes of hyperbilirubinemia in critically ill patients.

Case report: We present a 30-year-old woman with no past medical and drug history who was admitted to the intensive care unit (ICU) due to multiple trauma and fractures due to a fall from height. During the ICU stay, the patient developed jaundice with a high increase in the bilirubin level. A diagnosis of sepsis-associated cholestasis was considered after ruling out other possible pathologies. The hyperbilirubinemia improved with the early management of sepsis concomitant supportive medical therapy.

Conclusion: Early recognition and treatment of sepsis as a cause of cholestasis should be considered in ICU patients. Drugs targeting mitochondrial function would provide rapid hepatic recovery reducing complications and mortality.

Keywords: Cholestasis, Critical illness, Hyperbilirubinemia, Liver failure, Sepsis

Corresponding author: Prof. Mojtaba Mojtahedzadeh Department of Clinical Pharmacy, Tehran University of Medical Sciences, 16-Azar St., Enghelab Ave., Tehran 14176-14418, Iran.
Tel: +982166980467, Fax: +982166461178 E-mail: mojtahed@sina.tums.ac.ir

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INTRODUCTION

In clinical practice, hyperbilirubinemia is a common finding among hospitalized patients. It is defined as an abnormally high level of bilirubin in the body, which may due to increased production and/or impaired hepatic handling of bilirubin. Nevertheless, it is seen as an unusual laboratory abnormality with no obvious signs of hemolysis or symptoms of liver disease (1). There are other reasons for hyperbilirubinemia including hemolytic (pre-hepatic) such as hemolysis, heart failure, hypotension, hepatocellular (hepatic) such as Crigler-Najjar disease, Gilbert syndrome, pharmacologic toxicity and obstructive (post-hepatic) (2). Hyperbilirubinemia was found to be common in intensive care units (ICU) patients with a high rate of morbidity and mortality (3, 4). Major causes of hyperbilirubinemia in ICU settings include hypoxic insults leading to hepatocyte injury (ischemic cholestasis), sepsis, drug-induced, and parenteral nutrition (5). Sepsis associated cholestasis is one of the important causes of the development of secondary jaundice with a few detailed reports on critical illness. Here we present an ICU case of sepsis-associated cholestasis and also discuss the successful medical management of this patient.

CASE REPORT

A 30-year-old woman with chest and abdominal blunt trauma and multiple fractures due to the fall from a height was admitted to the ICU. She had no past medical or drug history. During the physical examination, the patient was alert and had spontaneous breathing at the time of admission. Respiratory rate (RR): 26/min, oxygen saturation: 100% with supplemental oxygen, blood pressure (BP): 149/104 mmHg, heart rate (HR): 115/min, and Glasgow coma scale (GCS): 15/15. She underwent two operations for the scapula, femoral, and tibia fractures corrections and splenectomy under general anesthesia. Basic laboratory data revealed anemia and mild leukocytosis. Blood sugar, renal function tests, liver enzymes, bilirubin (total and direct), alkaline phosphatase (ALP), and coagulation factors were within a normal range.

The patient developed jaundice with a high increase in bilirubin serum levels on day 7 of ICU admission: total bilirubin: 8.3, and direct bilirubin: 7.4 mg/dL. The liver function tests revealed a cholestatic pattern with a rise in ALP (460 IU/L) and normal transaminase. Liver injury or obstruction in the biliary ducts was not found in the ultrasound imaging. With the normal count of reticulocyte (1.5%) and serum lactate dehydrogenase (LDH) (200 IU/L), hemolysis was ruled out. Human immunodeficiency virus (HIV) serology, hepatitis B surface antigen, and hepatitis C antibody were all negative. At the same time, the patient developed fever, hypotension (BP: 90/68 mmHg), and tachycardia (HR: 102/min) with altered mental status (GCS: 12/15). Sepsis workup was performed immediately along with fluid resuscitation, and the broad-spectrum antibiotics were initiated as follows: Meropenem 2 g every 8 hours; Vancomycin 1 g every 12 hours; and Metronidazole 500 mg every 8 hours IV infusion. Suspected sepsis was confirmed for the patient by the new lab data: lactate level: 27 mg/dL, procalcitonin: 5.8 ng/mL, erythrocyte sedimentation rate (ESR): 56 mm/h, c-reactive protein (CRP):

92.1 mg/L, white blood cell (WBC): 21300 cells/mcL, platelets count: 178000, and neutrophil-lymphocyte ratio (NLR): 13%. The blood (×2) and urine cultures were negative. The patient also received Levocarnitine (L-carnitine) (1000 mg every 8 hours orally), N-acetyl-cysteine (NAC) (2 g every 8 hours IV), vitamin C (1 g every 6 hours IV), Lactulose (30 mL every 4 hours orally), and serum Albumin 5% as adjuvant therapy for sepsis-associated cholestasis. After the next 48 hours, the patient's clinical condition dramatically improved with a decline in bilirubin levels. On day 15, the patient was completely recovered from jaundice with a bilirubin level of 1.1 mg/dL, and the complete blood cell (CBC) and inflammatory markers were reported as normal. She was discharged from the ICU and moved to a surgical ward. After 5 months of follow up, she is completely asymptomatic with normal liver function tests.

DISCUSSION

Clinicians were confronted by the differential diagnosis and treatment of hyperbilirubinemia during hospitalization. One of the potential causes of jaundice in the ICU setting is drug-induced cholestasis, which usually occurs weeks or months after treatment starts (6). Sepsis-associated cholestasis is a diagnosis of exclusion that should be managed for jaundice in critically ill patients. The presence of increased serum bilirubin levels can be recognized. Sepsis can reduce canal transport, leading to intrahepatic cholestasis. Also, inhibition of Na+-K+-ATPase basolateral membrane activity, reduced basolateral membrane fluidity, down-regulation of transporters, and reduced Ntcp and Mrp2 functions may occur (7). The diagnosis of sepsis-related cholestasis in our case was made after excluding all potential causes of the patient's condition like hemolysis (high total bilirubin level) and drug-induced liver injury (elevation in ALT and AST more than five times from that of normal range). This was also confirmed by the elevated ALP, lactate, and inflammation biomarkers levels.

Since there is no specific medical therapy for cholestasis of sepsis, eradication of infection with proper supportive care should be considered (6, 8). Immediate treatment with crystalloid IV fluid with the appropriate antimicrobial agents is the key strategy for sepsis management (9). The selection of the antibiotics regimen was based on the sepsis with the abdominal origin in our case. Cholestasis has been shown to have mitochondrial tension, the creator of mitochondria, hepatic apoptosis, and the risk of reducing bacterial infections, exacerbating oxidative strain (10). Accordingly, supportive medical therapy was initiated for our patient to improve mitochondrial function and reverse tissue hypoxia proposed to be caused by sepsis. L-carnitine is a mitochondrial cofactor with a positive impact on oxidative stress, inflammation, and cholestatic liver injury (11, 12). NAC with the same mechanism of action is safe and effective for non-paracetamol liver injury (13). Ascorbic acid (vitamin C) as a cofactor for physiological reactions, with anti-oxidant properties may protect cells against infection-induced oxidative stress (14). All of these medications could have optimistic implications on hepatic injury and sepsis recovery in this case report. Ammonia is the main factor involved in hepatic encephalopathy pathogenesis, and the astrocytes are the most affected cells. Ammonia lowering agents such as Lactulose

improve the mental status in patients with liver injury (15).

CONCLUSION

Sepsis-associated cholestasis may be underdiagnosed among critically ill patients. Exclusion of other possible pathology of hyperbilirubinemia such as hemolysis, biliary obstruction, and drug-induction should be considered. Early recognition and management of sepsis concomitant supportive medical therapy targeting mitochondrial function would provide rapid recovery.

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REFERENCES

1. Okolicsanyi L, Nassuato G, Muraca M, Orlando R, Iemmolo RM, Lirussi F, et al., editors. Epidemiology of unconjugated hyperbilirubinemia: revisited. New York. Thieme Medical Publishers, Inc.2008.1040538.
2. Joseph A, Samant H, 2019. Jaundice. StatPearls Publishing. Treasure Island. https://www.ncbi.nlm.nih.gov/books/NBK430685/.
3. Kramer L, Jordan B, Druml W, Bauer P, Metnitz PG. Incidence and prognosis of early hepatic dysfunction in critically ill patients—a prospective multicenter study. Crit. Care Med. 2007;35(4):1099-e7.
4. Brienza N, Dalfino L, Cinnella G, Diele C, Bruno F, Fiore T. Jaundice in critical illness: promoting factors of a concealed reality. Intensive Care Med. 2006;32(2):267–74.
5. Lescot T, Karvellas C, Beaussier M, Magder S. Acquired liver injury in the intensive care unit. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2012;117(4):898-904.
6. Chand N, Sanyal AJ. Sepsis-induced cholestasis. Hepatology. 2007;45(1):230-41.
7. Moseley R. Sepsis-associated cholestasis. Elsevier; 1997.
8. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. Nat Clin Pract Gastr. 2006;3(10):574-85.
9. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304-77.
10. Horvatits T, Trauner M, Fuhrmann V. Hypoxic liver injury and cholestasis in critically ill patients. Curr Opin Crit Care. 2013;19(2):128-32.
11. Hiramatsu A, Aikata H, Uchikawa S, Ohya K, Kodama K, Nishida Y, et al. Levocarnitine use is associated with improvement in sarcopenia in patients with liver cirrhosis. Hepatology Communications. 2019;3(3):348-55.
12. Schulte RR, Madiwale MV, Flower A, Hochberg J, Burke MJ, McNeer JL, et al. Levocarnitine for asparaginase-induced hepatic injury: a multi-institutional case series and review of the literature. Leuk. 2018;59(10):2360-8.

13. Chughlay MF, Kramer N, Werfalli M, Spearman W, Engel ME, Cohen K. N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review protocol. Syst. Rev. 2015;4(1):84.
14. Marik PE. Vitamin C: an essential "stress hormone" during sepsis. J. Thorac. Dis. 2020;12(Suppl 1): S84.
15. Rose C. Ammonia-lowering strategies for the treatment of hepatic encephalopathy. Clin. Pharm. 2012;92(3):321-31.