LETTER TO THE EDITOR

Postoperative Hyperbilirubinemia and Acute Liver Dysfunction after Cytoreductive Surgery and HIPEC

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Dear Editor,

A 23-year-old-man weighing 53 kgs, with no comorbidities or addiction, who had been diagnosed with carcinoma of the appendix with pseudomyxoma peritonei was scheduled for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Preoperative investigations had shown a Hb 10.1 gm%, bilirubin of 0.4 mg/dL with AST – 30 U/L and ALT – 30 U/L, alkaline phosphatase – 209 U/L, albumin 3.69 gm/dL, globulin – 5.47 gm/dL and INR – 1.24. A thoracic epidural was inserted and standard general anesthesia was induced. The radial artery was cannulated and cardiac output monitoring was done. The right internal jugular vein was cannulated. The cytoreduction was completed and the total blood loss was 9000 mL. A total of 10.5 L of crystalloids, 2000 mL of 4% albumin, 1500 mL of gelatin, 2633 mL of packed red blood cells, and 1638 mL of fresh frozen plasma were transfused. Intraoperatively, the noradrenaline requirement went up to 0.8 µg/kg/min for 30 minutes. After CRS, HIPEC was given for 90 minutes with 23.5 mg of doxorubicin and mitomycin-C each. The minimum temperature (end of CRS) was 34.5°C and the maximum temperature during HIPEC was 37.5°C. The total urine output was 700 mL and the duration of the surgical procedure was 780 minutes. At the end of HIPEC phase ABG showed a pH of 7.22, bicarbonates of 18.9, and lactates increased to 6.45.

After the surgery, the patient was shifted for elective postoperative ventilation. On postoperative day (POD) 1, his investigations showed a bilirubin of 4.6 mg/dL (direct 3.56 mg/dL and indirect 1.10 gm/dL) with AST – 187 U/L, ALT – 65 U/L, INR – 1.59, aPTT – 39.9 seconds. Keeping in mind the normal increase in liver enzyme after a major CRS-HIPEC, the trachea was extubated on POD 1. In the evening laboratory reports showed a bilirubin of 13.43 mg/dL, (direct bilirubin 9.19 mg/dL, indirect 4.26 mg/dL), AST 266U/L, ALT 75U/L, INR – 1.44. ABG showed pH – 7.44, PCO_2 – 38.3 mm Hg, HCO3 – 25.5 mmoL/L, lactates – 1.49 mmoL/L on room air. The serum ammonia level was also sent, which was 72.9 µg/dL.

His Hepato-portal Doppler study showed normal portal vein diameter with normal color flow and respiratory phasic variation [peak systolic velocity (PSV) = 20]. The hepatic artery showed normal Doppler perceptible color flow and spectral indices (PSV = 35–40). The liver appeared normal in size and echotexture. Blood and urine were also sent for blood crossmatching-related reaction which came back negative. A negative Coombs test also suggested no transfusion-related reactions. On POD 2, his total bilirubin decreased to 5.84 mg/dL and indirect bilirubin to 1.96 mg/dL, direct bilirubin to 3.88 mg/dL. Bilirubin was on a decreasing trend thereafter.

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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is well established but associated with higher postoperative mortality and morbidity.[1] Transient changes in liver function are common after major surgery due to surgical stress and reduced hepatic blood flow from anesthesia and multiple blood transfusions.[2] Postoperative acute liver dysfunction leading to a very high value of serum bilirubin as in our case, after CRS-HIPEC is rare and not reported.

Evidence has shown that a long duration of anesthesia leading to the reduction in hepatic blood flow can cause an increase in the level of abnormal aminotransferases in conjunction with a normal abdominal ultrasound scan suggesting ischemic liver injury. The majority of anesthetics lead to a decrease in portal blood flow, which can cause a decrease in clearance of both endogenous and exogenous substances which have a high hepatic extraction ratio due to a decrease in flow. Even though there is an increase in hepatic arterial blood flow, it fails to maintain adequate oxygen supply during anesthesia along with blood loss and hypotension during surgery causing ischemic injury which can impair its normal function.[3] There are also cases of hyperammonemia reported after HIPEC. These are mostly seen with liver decompensation and can cause neurological deterioration which did not happen in our case.[4]

Less frequently reported were the warm chemotherapeutic drugs used during HIPEC as a cause of hepatotoxicity.[5] Warm chemotherapeutic agents along with their manipulation in proximity to the biliary tree can also be a contributory factor. Thermal injury may be caused by the direct placement of an inflow pump over the liver or the long duration of the HIPEC phase causing necrosis of

the hepatocytes secondary to heat.[5] The use of chemotherapeutic agents like adriamycin and mitomycin during HIPEC can cause local toxicity and necrosis of liver tissues by entrapment in the Glisson capsules. A rise in aminotransferases can occur with adriamycin but elevation of bilirubin and coagulopathy is rare.[6]

In this case, the preoperative clinical course showed no evidence of preoperative liver disease or extra or intrahepatic obstruction. Hemolytic reaction due to multiple blood transfusions was ruled out by a negative Coombs test. Intraoperative massive blood loss and the use of high doses of vasopressors for a short duration of time might have triggered the hypoxic injury to the hepatic tissues. The use of doxorubicin and mitomycin during the HIPEC phase might have added to the chances of liver dysfunction. Given the multifactorial nature of liver dysfunction, it can be challenging to pinpoint a single causative factor. Treatment and management would then be tailored based on the specific circumstances of the case.

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