CASE REPORT

Hyperammonemia after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Report of Three Cases with Unusual Presentation

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Abstract

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment modality for peritoneal surface malignancies. A variety of metabolic derangements have been reported in the perioperative period in these patients, most of which are a result of the complex interaction of peritoneal denudation, chemotherapy bath, and fluid imbalance. We report three cases of hyperammonemia-related neurological dysfunction seen in HIPEC patients. To the best of our knowledge, this is the first report of this presentation. Timely recognition of this condition needs a high degree of suspicion, and unless aggressively treated, is likely to be associated with poor outcome.

Keywords: Cytoreduction, Hyperammonemia, Hyperthermic chemotherapy.

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Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment offered to patients with peritoneal disease in selected disease subtypes. While the rationale for the modality has been offered since the late 20th century, familiarity with the perioperative physiologic stresses has helped make safe delivery feasible in many high-volume centers.

As the surgical indications of the HIPEC procedure continue to be defined for peritoneal surface involvement in various disease subtypes, perioperative management has become increasingly more standardized.[1] The HIPEC procedure is complex and associated with a higher rate of treatment-related morbidity in line with the use of chemotherapeutic drugs at high temperature.

From our institute's 6-year experience with the procedure, where more than 100 such surgeries were done, we here report three patients who developed sudden deterioration after their HIPEC procedure and isolated hyperammonemia was the common peculiar finding seen. We aim to highlight this rare unusual presentation.

This case report has been prepared as per CARE guidelines, and a written informed consent for the publication of data has been taken from kin of all patients.

Case Descriptions

Our institutional practice entails all patients to be seen by a multidisciplinary team (MDT), and patients are counselled regarding the pros and cons of the surgery. Eligible candidates for HIPEC are then re-assessed by the dedicated anesthesia and critical care team for preoperative optimization and continuity of care till discharge from critical care/high dependency unit. All patients were registered in locally adapted enhanced recovery pathway for CRS and HIPEC procedures. A thoracic epidural catheter was placed in all the patients, and anesthesia was induced with fentanyl, propofol, and vecuronium. Sevoflurane was used with oxygen and nitrous oxide for maintenance of anesthesia. Apart from standard and invasive anesthesia monitoring (like ECG, pulse oximetry, invasive blood pressure) and central venous pressure monitoring (cardiac output, cardiac index, stroke volume, stroke volume index, and stroke volume variation) were also measured using FloTrac™, and Vigileo monitor and goal-directed fluid therapy were instituted. Arterial blood gas monitoring including arterial lactate was measured intraoperatively. All these patients were shifted to the intensive care unit (ICU) for overnight elective ventilation. After consultation with dieticians, weight, and subjective global assessment appropriate total parenteral nutrition (TPN) containing glucose, lipids, amino acids, and electrolytes were continued till oral intake can be safely tolerated in all the patients. None of the patients experienced hyperammonemia in close succession to or related to starting parenteral nutrition. The details of the patients and perioperative course of all the patients are mentioned in Table 1.

Discussion

The CRS and HIPEC procedure entails the removal of involved peritoneum and affected organs, which can often involve multi-visceral resections. It improves disease-free survival in all

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Table 1: Summary of perioperative course and outcome of three patients

	Case 1	*Case 2*	*Case 3*
Age/gender	60 years/female	43 years/female	53 years/female
Comorbidities	Hypertension Type 2 diabetes mellitus	None	Morbid obesity (BMI 48 kg/m^2) Restrictive lung disease
Preoperative liver and renal function tests	Normal	Normal	Normal
Clinical history	Right flank pain, right para-colic gutter mucinous collection, Low-grade mucinous neoplasm on appendectomy	Sigmoid cancer: post-colectomy at another center with the limited peritoneal disease.	Evaluated for abdominal pain; high-volume disease diagnosed on CT scan
Histology	Low-grade mucinous neoplasm of the appendix, pseudomyxoma peritonei	Poorly differentiated adenocarcinoma	Mucinous adenocarcinoma; likely appendiceal; pseudomyxoma peritonei
Surgical procedure	Right hemicolectomy with pelvic peritonectomy, oophorectomy, excision of metastatic deposits over sigmoid mesentery, Glisson's capsule, falciform and diaphragm and cholecystectomy PCI-15; CC-0	Right iliac fossa mass excision, segmental ileal resection, and partial cystectomy and omentectomy PCI-3; CC-0	Total peritonectomy (pelvic + lateral + bilateral diaphragm) + TAH+BSO + subtotal colectomy + splenectomy + cholecystectomy + ileocolic stapled anastomosis + diversion ileostomy PCI-35, CC-0
Drugs used in HIPEC	Adriamycin 27.5 mg and mitomycin C 27.5 mg for 90 min	Oxaliplatin—480 mg for 60 min	Adriamycin-30 mg and mitomycin C—30 mg for 60 min
Blood loss (mL)	1800	2800	4200
Blood volume replaced with packed cells (mL)	478	760	1560
Shifting condition	Shifted to ICU on minimal vasopressor support	Shifted to ICU without vasopressor support	Shifted to ICU with vasopressor support
First postoperative week	Shifted to the ward on POD2, early postoperative recovery good, on a soft oral diet	Subcutaneous hematoma over surgical incision; needed evacuation	While intubated due to weaning failure patient had generalized tonic-clonic seizures on POD 5
Second postoperative week	POD7-inattention and disorientation; sudden neurological deterioration to loss of consciousness, shifted to ICU, intubated and ventilated. Broad-spectrum antibiotic and antiviral started	POD 15-disorientation, no response to verbal command, pupils-bilateral equal and reactive to light Empirical antibiotic treatment instated	Persistent seizures despite neuroprotective measures Remained on antibiotic therapy in ICU
Liver function tests	Bilirubin 0.65 mg/dL Serum AST 34 U/L Serum ALT 43 U/L	Bilirubin 3.60 mg/dL Serum AST 283 U/L Serum ALT 70 U/L Normal	Bilirubin 1.6 mg/dL Serum AST 57 U/L Serum ALT 40 U/L
Hemoglobin trend	Normal	13600/mm^3 on POD-15 (ICU admission)	Normal
White cell count	Normal	Normal	Normal
Renal function test	Normal	USG liver-normal	Normal
Abdominal radiological tests	CT thorax, abdomen and pelvis No infective focus/shunt	CT abdomen-no porto-systemic shunts	CT abdomen-normal
Brain radiological findings	CT brain suggestive of globus pallidus lesion, rest findings normal MRI brain-restrictive diffusion of the cortical and subcortical layer; cytotoxic edema (Figs 1A to C)	No focal lesions on CT scan	CT brain showed diffuse cerebral edema (Fig. 1D)
Cultures	No growth in blood/urine	Ascitic fluid-heavy growth of *E. coli* (patient had intra-op contamination from bowel)	No growth in blood/urine
Further course	Developed status epilepticus, on EEG—no seizure activity, CSF examination—no sign of infection Had features of raised intracranial pressure, which were treated with neuroprotective measures but never completely resolved Developed MODS	Procalcitonin 1.9 ng/mL Slow improvement in blood investigations coupled with clinical recovery	GCS dropped to 3 on POD-8; supportive measures including renal replacement therapy continued

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	Case 1	*Case 2*	*Case 3*
Outcome	The patient succumbed on POD15	Proceeded to MODS and had a 2-week ICU stay but showed complete recovery	Clinical brain death; likely metabolic cause; patient succumbed on POD-9
Serum ammonia (µmol/L)	1300 (POD-10)	292 (POD-17)	2490 (POD-7)
Serial serum ammonia (µmol/L)	890 (POD-13)		613 (POD-9)
Serial serum ammonia (µmol/L)	500 (POD-15)		–
Peri-event AKI	No	No	No
C-reactive protein	Not measured	24 mg/dL	1.8 mg/dL

ASA: American Society of Anesthesiologist; AKI: acute kidney injury; ALT: alanine transaminase; AST: aspartate transaminase; CEA: carcinoembryonic antigen; CC: completion cytoreduction; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalogram; GCS: Glasgow coma scale; ICU: intensive care unit; MODS: multiple organ dysfunction syndromes; MRI: magnetic resonance imaging; PCI: peritoneal carcinomatosis index; POD: postoperative day

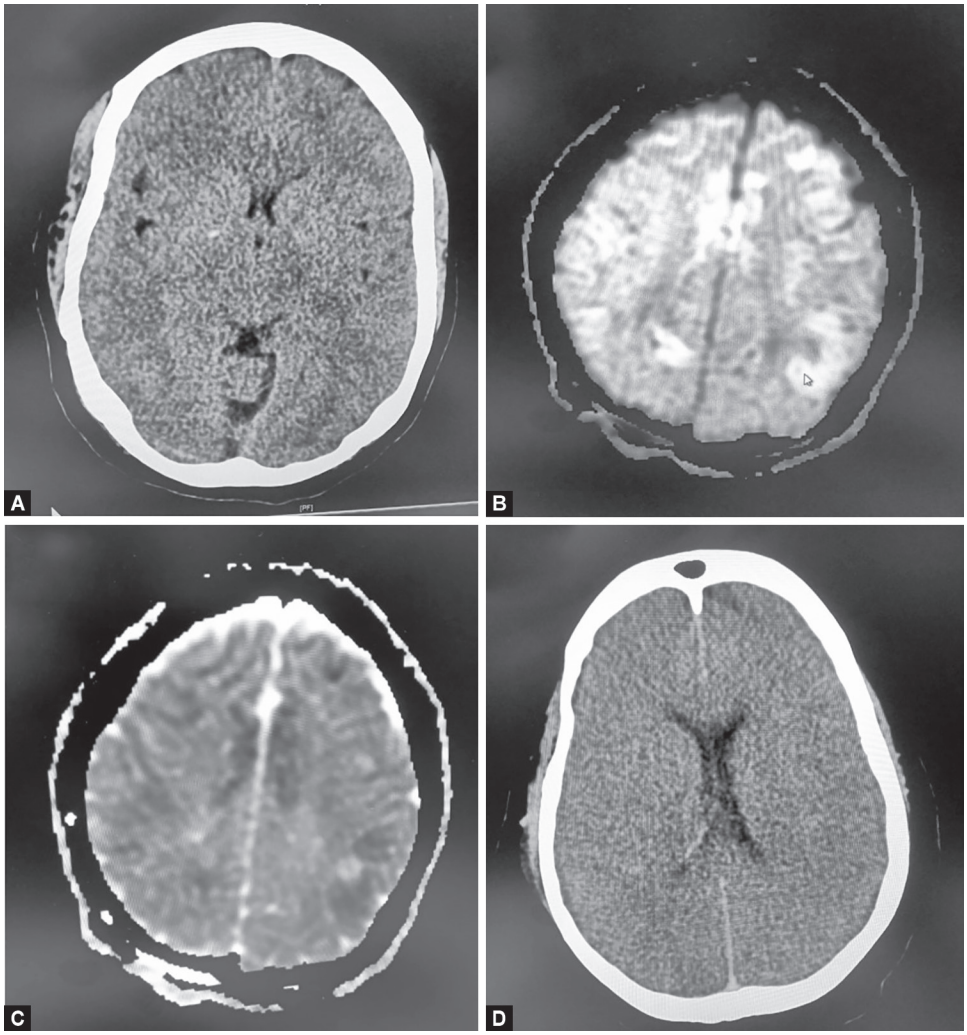

Fig. 1: (A) CT scan image of Case 1 shows tiny lesion at globus pallidus; **(B)** and **(C)** MRI image of Case 1 show diffusion and ADC images, respectively, show restrictive diffusion of the cortical and subcortical layer suggestive of cytotoxic edema; **(D)** CT scan image of Case 3 shows diffuse brain edema

subsites and with an improved understanding of operative and perioperative management, is slowly becoming an integral part of the management of peritoneal involvement in primaries of these subsites.

The perioperative management has now standardized,[1] and few complications of the procedure have been studied in the past.[2] To the best of our knowledge, this is the first report of hyperammonemia-associated neurological deterioration in patients after CRS and HIPEC.

Hyperammonemia is a metabolic derangement which can be seen with a variety of diseases.[3] In the surgical patient, it is commonly seen in liver decompensation or patients on high amino acid TPN treatment. In the ICU setup, hyperammonemia is associated with a high rate of morbidity and mortality.[4] None of the three patients we report had any known inherited error of metabolism, had no similar episodes in times of physiological stress like childbirth (as is seen in some unmasking of urea cycle defects), and preemptive screening for the same was not offered. All denied alcohol intake, and none had any coexistent liver illness or other precipitants. Patients 1 and 2 were on a liquid diet when they developed the neurological deterioration, and patient 3 had her TPN stopped. Hence, in all three patients, the role of TPN was not found contributory. Among chemotherapy agents, 5 fluorouracil has been reported to be associated with hyperammonemia, and its infusion has been reported to be associated with impaired consciousness in such cohort.[5] None of the three patients we report had use of any contributory drugs either. Also, while seizures can be associated with hyperammonemia, the correlation is suspected to be more likely due to muscle contraction than of causality.[6] The episode of deterioration was not associated with any acute kidney injury, fall in hemoglobin or hematocrit levels, or derangement of liver function. We hence hypothesize that the elevated ammonia levels in the patients were a finding unrelated to the seizures they developed and more likely associated with a possible unidentified etiology. In the body, serum ammonia levels more than 200 µmol/L are commonly associated with neurological symptoms, and if uncorrected can lead to the development of cerebral edema. The condition we report is likely a kind of non-cirrhotic hyperammonemia, recognition of which should direct aggressive supportive measures.[7–11] We ruled out potential infective causes, and treated them on the lines of hepatic failure and associated encephalopathic presentations. Early recognition and aggressive intervention with neuro- and hepatoprotective measures might offer patients a chance of recovery. The management strategy is focused at (a) ruling out coexistent confounding conditions like urinary infection with urease-producing organisms, gastrointestinal bleeding and drugs; (b) measures to decrease ammonia production in the gut by judicious use of antibiotics like rifaximin, increase gut transit using lactulose; (c) maintaining high energy intake; and (d) eliminating blood ammonia by hemodialysis as necessary. In the setting of raised intracranial pressure, supportive measures to decrease the same with the appropriate use of antiepileptics are advisable. High amino acid content in parenteral nutrition must be reviewed although we must be mindful that there is insufficient evidence to support the use of zero protein enteral diet.[9–11]

In conclusion, this is the first report of non-cirrhotic hyperammonemia in HIPEC patients. A high index of suspicion is warranted, and levels of ammonia should be evaluated in any patient with sudden neurological deterioration when other parameters remain within normal limits. Wherever available, amino acid estimations can be offered to rule out adult-onset metabolic disorders.

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