Hyperammonemic encephalopathy associated with 5-fluorouracil in a patient with previous orthotopic liver transplantation

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ABSTRACT

5-Fluorouracil (5-FU)-based chemotherapy is the most common regimen used to treat metastatic or advanced colon cancer. Neurotoxicity is a rare but serious adverse effect of 5-FU-based therapy. We report an unusual case of 5-FU-induced hyperammonemic encephalopathy in a patient with recurrent colon cancer that metastasized to the liver and lung. Two days after receiving the third dose of FOLFOX, he presented with altered mental status, agitation, abdominal pain, nausea, and vomiting. His total ammonia level was 434 $\mu\text{mol/L}$, for which he was treated with lactulose retention enema and lactulose via nasogastric tube. Over the next 24 hours, his condition improved significantly.

KEYWORDS Colon cancer; 5-fluorouracil; hyperammonemic encephalopathy

Colorectal cancer is the second leading cause of cancer-related death in the United States.¹ Systemic chemotherapy with 5-fluorouracil (5-FU)-based chemotherapy is a commonly used primary regimen to treat metastatic or advanced colon cancer.² Therapy with 5-FU is associated with a wide range of adverse effects, including bone marrow suppression leading to thrombocytopenia and neutropenia and gastrointestinal side effects such as nausea, vomiting, and diarrhea. A more rare but serious adverse effect of 5-FU is neurological toxicity secondary to hyperammonemia.^{3,4} Encephalopathy secondary to 5-FU has a reported incidence of 5.7% to 8.7% in patients treated with high-dose 5-FU infusion (2600 mg/m^2 over 24 hours, every week).^{5,6} We report a case of severe hyperammonemic encephalopathy shortly after initiation of combination chemotherapy with 5-FU for metastatic colon cancer.

CASE REPORT

A 66-year-old man with a known history of colon cancer treated with a right hemicolectomy and orthotopic liver

transplantation secondary to hepatitis C and alcoholic cirrhosis was found to have recurrent colorectal metastases to the liver and lung. Adjuvant chemotherapy consisting of FOLFOX (5-FU, oxaliplatin, folinic acid) and bevacizumab was initiated. Fluorouracil was given as a 400 mg/m^2 intravenous infusion on day 1, followed by 1200 $\text{mg/m}^2/\text{day} \times 2$ days (total 2400 mg/m^2 over 46–48 hours). At baseline, the patient had normal liver function tests, with an alanine aminotransferase of 15 U/L; aspartate aminotransferase, 33 U/L; alkaline phosphatase, 66 U/L; albumin, 3.7 g/dL; total bilirubin, 0.7 mg/dL; platelets, 218/ μL ; prothrombin time, 12.2 seconds; and international normalized ratio, 1.0. Two days after receiving the third dose of chemotherapy, he presented to the emergency department with altered mental status, agitation, abdominal pain, nausea, and vomiting. According to the patient's wife, symptoms had begun abruptly 3 hours earlier and included five to seven bilious, nonbloody vomiting episodes. On examination, the patient was afebrile, normotensive, and slightly tachycardic with a blood pressure of 130/85 mm Hg and heart rate of 105 beats per minute. Respirations were nonlabored with 17 breaths/minute. The patient's mucous membranes were moist with normal skin

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turgor. On neurologic exam, cognitive abnormalities were present with disorientation to person, place, and time. An abdominal series and computed tomography of the head showed no evidence of abnormalities. Electrolytes and liver function tests were all within normal limits, but the patient's venous blood ammonia level was significantly elevated at 434 $\mu\text{mol/L}$ (normal, 11–32 $\mu\text{mol/L}$). He had nonoliguric acute kidney injury (blood urea nitrogen, 30 mg/dL; creatinine, 1.76 mg/dL). His white blood count was within normal limits at 6.8/ μL .

The patient's 5-FU infusion was stopped immediately and intravenous hydration was started. He was diagnosed with grade III hepatic encephalopathy and transferred to the intensive care unit, where he received rifaximin 500 mg twice daily, lactulose 200 g retention enema, and lactulose (30 g/45 mL) via nasogastric tube. Despite a low suspicion for sepsis, cultures were taken and he was placed on broad-spectrum antibiotics. Within 24 hours of fluid resuscitation and lactulose treatment, his blood ammonia levels decreased to normal limits and his acute kidney injury and encephalopathy resolved. His chemotherapy regimen dose was cut in half, and he was prescribed daily oral lactulose treatment. Afterwards, he experienced no more neurological complications.

DISCUSSION

Neurotoxicity is a rare adverse effect of 5-FU chemotherapy.^{7,8} Some case reports have reported noncirrhotic hyperammonemic encephalopathy after initiation of 5-FU–based chemotherapy.^{9–15} The diagnostic criteria for 5-FU–induced encephalopathy consist of development of encephalopathy during or shortly after completion of 5-FU administration and exclusion of other medications or factors (e.g., liver failure) contributing to encephalopathy.

The biological basis for 5-FU–induced encephalopathy is not completely understood, but multiple pathways have been proposed. The mechanism that most likely contributed to this patient's encephalopathy is accumulation of toxic byproducts of 5-FU catabolism. For example, fluorocitrate, the final metabolite of 5-FU, has been shown to inhibit aconitase, a Krebs cycle enzyme.¹⁶ The Krebs cycle shares several intermediates with the urea cycle, the pathway responsible for converting highly toxic ammonia to urea.¹⁷ Therefore, inhibition of the Krebs cycle by 5-FU metabolites can impair the urea cycle, resulting in accumulation of ammonia and lactic acidosis. It is important for physicians to closely monitor the neurological status of their patients after initiation of

treatment and be aware of hyperammonemic encephalopathy as a possible adverse effect of 5-FU therapy.

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