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Hyperammonemia Secondary to 5-Fluorouracil

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

5-fluorouracil (5-FU) is one of the most common adjuvant antineoplastic agents used in the treatment of localized and metastatic colon cancer. Frequent side effects of 5-FU include myelosuppression, mucositis, nausea, vomiting, and diarrhea. However, hyperammonemic encephalopathy is a rare neurologic toxicity that can occur after 5-FU chemotherapy administration. Patients with 5-FU–induced hyperammonemic encephalopathy often exhibit symptoms of altered mental status with no radiologic abnormalities or laboratory abnormalities except for significantly elevated ammonia levels with occasional lactic acidosis and respiratory alkalosis. We report a case of a patient with stage IV colon adenocarcinoma who experienced altered state of consciousness due to hyperammonemia during the administration of palliative chemotherapy with 5-FU, bevacizumab, and leucovorin. On cycle 1 day 2 of chemotherapy, the patient became drowsy and confused at home, prompting a visit to the emergency department and ultimately hospital admission. Laboratory tests revealed an elevated blood ammonia level (838 µg/dL). After an extensive negative workup, his altered state of consciousness was thought to be secondary to 5-FU–induced hyperammonemia. Upon admission, 5-FU was immediately discontinued and the patient was treated with lactulose enemas, intravenous fluids, rifaximin, and continuous renal replacement therapy with gradual recovery to baseline mental status. It is crucial for advanced practitioners to be aware of this rare side effect to ensure prompt diagnosis and maximize treatment effectiveness.

CASE STUDY

Our patient is a 65-year-old male who was previously diagnosed with non-secretory lambda light chain multiple myeloma in 2007. He initially received induction chemotherapy with bortezomib and later underwent autologous stem cell transplant in 2008, which was complicated by fluid retention and debilitating neuropathy. He achieved only partial disease response with persistent clonality on his serum free light chains. He was

started on maintenance therapy with lenalidomide in June 2011; however, lenalidomide was later discontinued in 2013 due to worsening renal function requiring initiation of home peritoneal dialysis. The patient remained in partial remission and continued serial follow-ups including PET scans, which did not show any evidence of myeloma progression.

In November 2021, the patient was found to have asymptomatic anemia with a hemoglobin of 6.8 g/dL. Iron studies were collected, which were within normal range. Myeloma light chain studies were essentially unchanged. In January 2022, the patient began experiencing symptoms of progressively increasing generalized weakness, fatigue, and hematochezia. He was hospitalized and discovered to have recurrent anemia with a hemoglobin of 7.2 g/dL. He underwent a colonoscopy revealing an ulcerated obstructing stricture in the mid descending colon with ulceration and ischemia involving the entire circumference of the colon. Biopsies were collected approximately 45 cm from the anal verge, and pathology results confirmed the diagnosis of left-sided descending colon adenocarcinoma, microsatellite stable (MSS).

In February 2022, the patient underwent an initial staging CT scan of the chest/abdomen/pelvis, which was concerning for liver metastasis. A PET/CT scan was performed for further evaluation, and the patient was found to have an isolated left hepatic lobe metastasis. *KRAS* results were pending; therefore, the patient was initiated on therapy consisting of standard dosed bevacizumab 5 mg/kg, leucovorin 400 mg/m^2, and 5-fluorouracil (5-FU) in a 400 mg/m^2 bolus and 2,400 mg/m^2 by continuous infusion for 3 days (oxaliplatin could not be used due to the patient's chronic severe neuropathy). Additionally, given the patient's end-stage renal disease (ESRD) requiring home peritoneal dialysis 5 days per week, it was decided not to use the leucovorin, 5-FU, and irinotecan (FOLFIRI) regimen, as irinotecan is not recommended for patients with ESRD.

The patient began cycle 1 of chemotherapy with bevacizumab plus 5-FU in March 2022. Upon returning home after chemotherapy, he began experiencing persistent, severe nausea and vomiting. He was later admitted to the progressive care unit on cycle 1 day 2 of chemotherapy with increasing lethargy and altered mental status. Upon physical exam, the patient was confused and lethargic but otherwise without any appreciable unilateral weakness or facial drooping. The cardiac, respiratory, and abdominal exam was unremarkable. A stroke workup was completed including a CT of the brain, which was negative, CT cerebral perfusion study, which showed no evidence of ischemia, and CT angiography of head/neck, which did not reveal any evidence of stenosis or thrombus. Vital signs did not reveal any abnormalities, and there were no other neurologic deficits.

Table 1 depicts laboratory results upon admission. On initial arterial blood gas analysis, carbon dioxide levels were within normal range and oxygen was slightly elevated at 109; there was no evidence of acidemia or alkalosis (pH 7.408, bicarbonate 23.3). Laboratory results revealed that the patient's ammonia level was markedly increased to 838 µg/dL, but all other liver function tests were within normal range. His creatinine level was at baseline, 8.08 mg/dL compared with 8.3 mg/dL 1 week prior to chemotherapy.

Upon admission, we immediately stopped infusion of 5-FU. He continued to become more lethargic and unresponsive, ultimately

Table 1. Initial Laboratory Results

ABG	CBC	Chemistry
pH: 7.408	**WBC:** 5.55 × 10^3/µL	**Sodium:** 136 mmol/L
pCO_2: 33.0 mmHg	**Hemoglobin:** 9.9 g/dL	**Potassium:** 7.9 mmol/L
pO_2: 109 mmHg	**Hematocrit:** 31.3%	**BUN:** 70 mg/dL
HCO_3: 23.3 mmHg	**MCV:** 87.2 fL	**Creatinine:** 8.08 mg/dL
	Platelets: 175,000/µL	**Calcium:** 9.2 mg/dL
		Lactic acid: 23.7 mmol/L
		Phosphorus: 5.7 mg/dL

Note. Initial laboratory results are from day 1 of hospital admission (cycle 1 day 2 of bevacizumab plus 5-FU). Other laboratory results were not included as they were within normal limits. ABG = arterial blood gas; CBC = complete blood count; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; HCO_3 = bicarbonate; WBC = white blood count; MCV = mean corpuscular volume; BUN = blood urea nitrogen.

requiring intubation and transfer to the intensive care unit. On day 2 of hospitalization, the patient experienced cardiac arrest, so advanced cardiac life support was initiated with return of spontaneous circulation (ROSC). Following cardiac arrest and ROSC, the patient was initiated on continuous renal replacement therapy (CRRT). An electroencephalogram revealed moderately severe diffuse encephalopathy with triphasics as seen with metabolic abnormalities. Ammonia level trends are depicted in Figure 1. By day 5 of hospitalization, the patient's ammonia level had improved to < 15 µg/dL after treatment with lactulose enemas, intravenous fluids, rifaximin, and CRRT. He was later extubated on day 7 of hospitalization, and CRRT was transitioned to hemodialysis. The patient was later discharged to inpatient rehabilitation after being hospitalized for 21 days.

Other reasons for hyperammonemic encephalopathy such as liver disease, drug abuse, and alcohol abuse were ruled out. The patient's creatinine was at baseline upon admission, and all liver function tests were within normal limits. The urine drug screen was positive for opiates; however, the patient had been taking oral hydromorphone as prescribed. Consideration was also given to rare instances of dihydropyrimidine dehydrogenase (DPD) deficiency, but this was also ruled out as the patient had no signs or symptoms of DPD deficiency such as neutropenia, thrombocytopenia, or mucositis. There are also rare case reports describing hyperammonemia in patients with progressive multiple myeloma; however, this was ruled out in this particular case given that the patient's myeloma remained in partial remission as evidenced by negative serology and PET scan with no evidence of myeloma progression. Therefore, after ruling out other causes, it was determined that our patient had 5-FU–induced hyperammonemic encephalopathy.

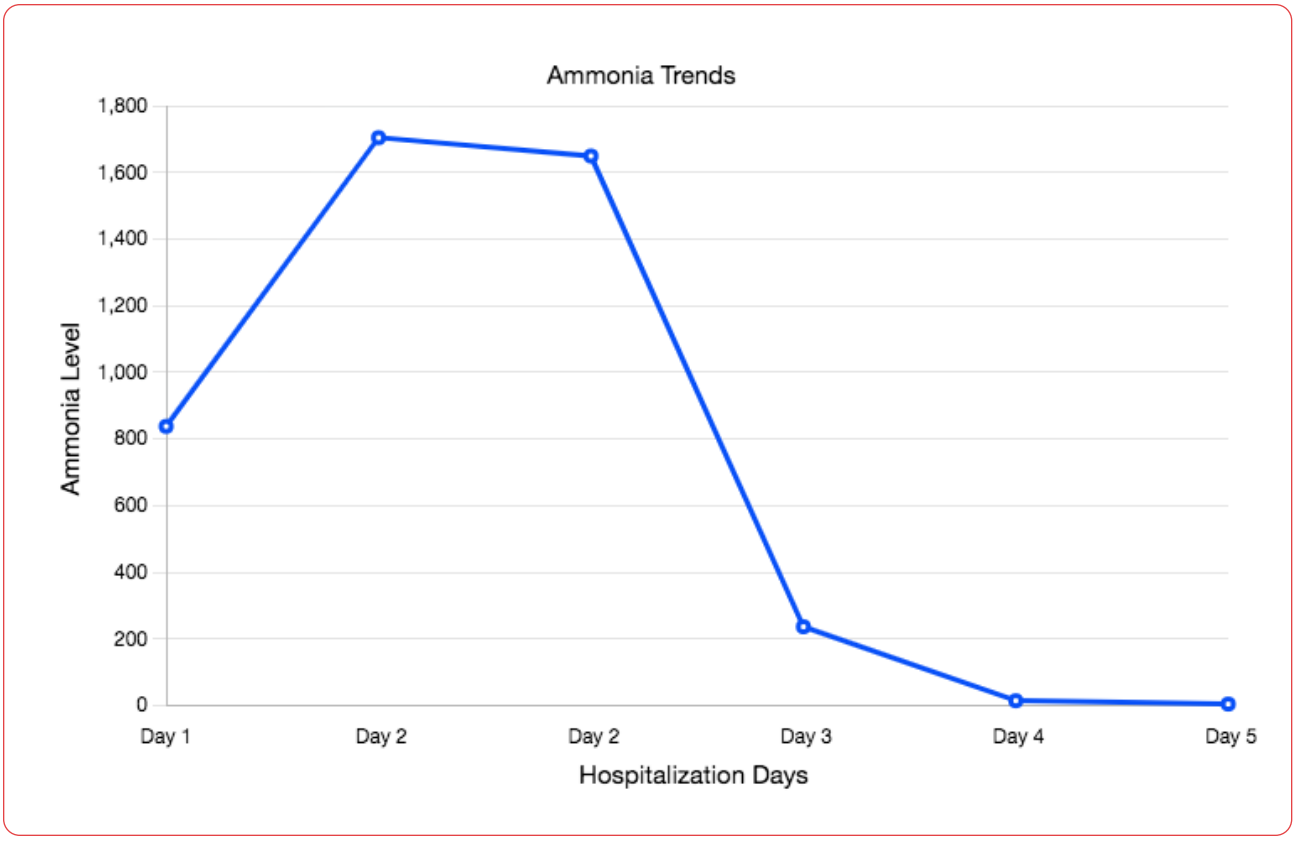

Figure 1. Ammonia level trends during day 1 of hospitalization through day 5 of hospitalization when ammonia level normalized. The following are the ammonia values respectively: 838 µg/dL (day 1), 1,704 µg/dL (day 2 AM), 1,649 µg/dL (day 2 PM), 237 µg/dL (day 3), 15 µg/dL (day 4), < 15 µg/dL (day 5).

Colorectal cancer is the third most prevalent malignancy in the United States and is one of the leading causes of cancer-related mortality (Islami et al., 2021). Compared to other gastrointestinal (GI) malignancies, colon cancer has demonstrated fairly good response to chemotherapy both in the neoadjuvant, adjuvant, and palliative settings.

The antineoplastic agent, 5-fluorouracil (5-FU), is one of the most common chemotherapies used in the treatment of localized and metastatic colon cancer as well as several other tumor types such as pancreatic, head and neck, gastric, rectal, and occasionally breast cancers. This antimetabolite antineoplastic agent is a fluorinated pyrimidine analog and cell cycle S-phase–specific, inhibiting the conversion of deoxyuridylic acid to thymidylic acid by blocking thymidylate synthetase, thus interfering with DNA synthesis (Chmielowski & Territo, 2017; Yarbro et al., 2018). Metabolites of 5-FU are also incorporated into RNA and interfere with RNA function and protein synthesis (Chmielowski & Territo, 2017). Subsequently, 5-FU undergoes extensive intracellular activation via a series of enzymes, primarily including dihydropyrimidine dehydrogenase (DPD). Therefore, patients with DPD deficiency can experience severe 5-FU toxicity due to excessive accumulation of 5-FU in the body (Chmielowski & Territo, 2017). Frequent side effects of 5-FU include myelosuppression, mucositis, nausea, vomiting, and diarrhea (Yarbro et al., 2018). Hyperammonemic encephalopathy is a rare neurologic toxicity that can occur after 5-FU chemotherapy administration. Patients with 5-FU–induced hyperammonemic encephalopathy often exhibit symptoms of altered mental status with no radiologic abnormalities or laboratory abnormalities except for significantly elevated ammonia levels with occasional lactic acidosis and respiratory alkalosis (Thomas et al., 2015).

DISCUSSION

Hyperammonemia is a rare but serious and sometimes fatal side effect of 5-FU–based chemotherapy. If recognized early enough and treated correctly, patients can return back to baseline fairly quickly. In this case, the patient's family promptly recognized the patient's acute change in mental status with increasing lethargy and immediately notified emergency medical services who transported the patient to the emergency department. Initially, we treated the patient for hyperammonemia without being certain of the primary cause. After further research, we discovered the rare side effect of 5-FU–induced hyperammonemia.

The reported incidence of 5-FU–induced hyperammonemia is 0.7% to 5.7% (Nakamura et al., 2020). Its exact etiology is still uncertain (Nakamura et al., 2020). It has been postulated that one of the catabolites of 5-FU, fluoroacetate, directly suppresses the Krebs cycle, resulting in dysfunction of the ATP-dependent urea cycle. Thus, the conversion of ammonia to urea is prevented, leading to excess accumulation of ammonia (Mitani et al., 2017). Another presumed cause of hyperammonemia is related to DPD deficiency, which is reported in 2.7% of cancer patients (Yi et al., 2016). With DPD deficiency, 5-FU catabolism does not occur, which leads to excessive 5-FU accumulation within the body. Excess 5-FU can penetrate into the cerebrospinal fluid causing neurotoxic effects such as acute demyelination of neurons and can also increase cellular metabolism leading to Wernicke encephalopathy (Yi et al., 2016). Throughout our extensive literature review, we could not find any relationships between the dose of 5-FU and the incidence of hyperammonemia.

Some of the risk factors for 5-FU–induced hyperammonemia include hypoalbuminemia, renal dysfunction, dehydration, constipation, anemia, and infection. Measurement of DPD levels was not a readily available standard test in our facility, so we elected not to collect DPD level analysis, as our patient was not exhibiting any mucositis, neutropenia, or thrombocytopenia, which are invariable findings of DPD deficiency. However, we can say that our patient was at increased risk given possible dehydration from intractable nausea/vomiting. His end-stage renal disease could have also contributed to the development of 5-FU hyperammonemia; however, it is difficult to definitively say that his renal dysfunction was the primary cause given that his creatinine was at baseline and 5-FU was dose reduced based on his baseline renal function.

TREATMENT

Treatment for patients who experience 5-FU–induced hyperammonemia includes immediate

discontinuation of 5-FU, intravenous fluid hydration, and lactulose enemas (Yi et al., 2016). Other studies also reported that branch-chained amino acids showed excellent results in treatment of 5-FU–induced hyperammonemia (Yi et al., 2016). In this case, 5-FU was immediately discontinued, and our patient was treated with intravenous fluids, lactulose enemas, rifaximin, and continuous renal replacement therapy with subsequent improvement in ammonia level (< 15 µg/dL) and mental status.

Case reports suggest alternatives for colon cancer treatment, which include a 50% dose reduction of continuous 5-FU or switching to capecitabine, an oral form of 5-FU to prevent recurrence of hyperammonemia (Mitani et al., 2017). Since our patient had end-stage renal disease, capecitabine was contraindicated given its predominant renal clearance, and we did not want to rechallenge 5-FU. Therefore, we decided that the patient would be transitioned to panitumumab once his performance status improved following hospitalization and completion of inpatient rehabilitation.

CONCLUSION

Hyperammonemia is a rare but serious side effect that can occur after administration of 5-FU–based chemotherapy. If not diagnosed and treated quickly, the result can be detrimental. Therefore, it is imperative for advanced practitioners to be cognizant of the early signs and symptoms of 5-FU–induced hyperammonemia such as altered mental status, lethargy, and persistent nausea/vomiting, which usually occur within the first 1 to 3 days of 5-FU administration. Laboratory tests and neurologic workup should be performed to rule out other causes for altered mental status; however, when neurologic workup is negative and a patient is without any laboratory abnormalities apart from hyperammonemia, the diagnosis of 5-FU–induced hyperammonemia should be considered. Treatments for these patients include immediate discontinuation of 5-FU, intravenous fluid hydration, lactulose enemas, branch-chained amino acids, and hemodialysis or continuous renal replacement therapy if necessary. It is crucial for advanced practitioners to be aware of this rare side effect to ensure prompt diagnosis and effective treatment.

Disclosure

The author has no conflicts of interest to disclose.

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