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Case Report

A case of acute hyperammonemic encephalopathy after initiation of 5-fluorouracil chemotherapy

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ABSTRACT

5-fluorouracil is a chemotherapeutic agent that has been used for decades to treat a number of neoplasms. It has a number of adverse effects; however, we present a case of a seldom reported side effect in hyperammonemic encephalopathy that should be considered in patients presenting with altered mental status shortly after starting therapy.

Keywords: 5-Fluorouracil, Chemotherapy, Adenocarcinoma, Hyperammonemia, Encephalopathy

INTRODUCTION

5-fluorouracil (5-FU) is a cytotoxic chemotherapeutic agent that has been used since 1947 in the treatment of anal, breast, colorectal, esophageal, stomach, pancreatic, head and neck, and skin cancers.[1] Common adverse effects include gastrointestinal upset, mucositis, myelosuppression, hand-foot syndrome, and, less commonly, cardiotoxicity.[2] Here, we present a rare case of 5-FU induced hyperammonemic encephalopathy in a patient shortly after chemotherapy was administered.

CASE REPORT

An 80-year-old female with a medical history of chronic kidney disease stage (CKD) IIIb, chronic anemia, and invasive rectal adenocarcinoma (T4aN1), diagnosed 1 month prior presented to the emergency department with worsening abdominal pain, nausea, and vomiting 24 h after her first FOLFOX 6 (Leukovorin calcium 400 mg/m^2, fluorouracil 400 mg/m^2 followed by 1200 mg/m^2 continuous infusion every 24 h for the following 24 h, and oxaliplatin 85 mg/m^2) intravenous chemotherapy cycle. She was still receiving the 5-FU infusion through her computerized ambulatory delivery device on presentation. The patient was hypertensive on arrival with a blood pressure of 181/90 mmHg, a Glasgow Coma Scale (GCS) of 15, and was alert and oriented x three. Shortly after, the patient became progressively more confused, and she developed left lateral eye deviation. She was ultimately intubated for airway protection due to worsening somnolence and encephalopathy with a GCS of 5. Laboratory findings were notable for a severely elevated ammonia level of 586 μmol/L with normal liver function tests, an anion gap metabolic acidosis with respiratory alkalosis secondary to overcompensation in the setting of lactic acidosis, and acute kidney injury. Computed tomography angiography head and neck were negative for any

abnormalities. Computed tomography chest, abdomen, and pelvis showed a slight interval increase in the right rectal wall mass, but no acute processes. Treatment was initiated with lactulose, sodium bicarbonate infusion, and intravenous fluids. The 5-FU infusion was discontinued. Encephalopathy workup including brain magnetic resonance imaging, continuous video electroencephalography monitoring, and toxic alcohols was all negative. On hospital day 2, the patient's mental status improved back to her baseline, GCS improved to 15, her ammonia level decreased to 26 μmol/L, and she was successfully extubated. Her next treatment was skipped 2 weeks later; however, she was agreeable to trialing a lower dose of treatment soon thereafter. The FOLFOX 6 regimen was given without the 5-FU or leucovorin boluses, and the dose of the 5-FU was decreased. The 5-FU infusion was started gradually at 400 mg/m^2, and up titrated to 600 mg/m^2 every 24 h for 46 h. At the next follow-up, the 5-FU dose was increased to 800 mg/m^2 every 24 h for 46 h with a flat dose of 400 mg/m^2. Her next two 5-FU doses were increased to 1000 mg/m^2 and oxaliplatin was renally adjusted to 65 mg/m^2. Unfortunately, after the second dose, the patient became encephalopathic and her ammonia was found to have increased again to 523 μmol/L. The patient was able to be managed outside of the Intensive Care Unit with up titration of lactulose, and her ammonia decreased to 27 μmol/L. The patient has since been managed on a constant reduced dose rate of 200 mg/m^2 with lactulose and is tolerating it well.

DISCUSSION

Acute hyperammonemic encephalopathy is a rare complication of 5-FU that has been described in case reports, small cohorts, and one national survey of 30 patients in France.[3] It is also mentioned under the "Warning and Precautions" section of US FDA approved label for 5-FU. Typical reports describe patients without prior liver disease who develop signs and symptoms of encephalopathy (altered mental status, confusion, ataxia, disorientation, or coma) with concomitant hyperammonemic encephalopathy within 72 h of 5-FU administration.[3] The incidence of this adverse effect is unknown, though it is estimated to occur in 0.002–1.1% of patients treated with 5-FU, and increases to 5.7% with higher dosages (2600 mg/mL/week). It is possible that poor clinician awareness of this phenomenon has led to under-detection.[3,4] Renal failure, sarcopenia, infection, lymphopenia, low red blood cell count, hypoalbuminemia, constipation, and dehydration all appear to increase the risk of this adverse effect.[3,5]

Although the mechanism through which 5-FU can cause hyperammonemia is currently unknown, a leading theory is that fluoroacetate, a 5-FU catabolite, may inhibit the Krebs cycle, thus decreasing ATP production, inhibiting the urea cycle and impairing the body's ability to clear ammonia.[3] Approximately 20% of 5-FU follows an anabolic pathway that leads to its chemotherapeutically beneficial cytotoxicity. The remaining 80% is catabolized in the liver by dihydropyrimidine dehydrogenase (DPD) into ammonia, fluoroacetate, and other metabolites that are then renally eliminated.[3,5] A few case reports of patients with dialysis-dependent renal failure who developed hyperammonemic encephalopathy following 5-FU treatment show increased blood levels of fluoroacetate during episodes of encephalopathy, and the increased risk of hyperammonemia in patients with renal failure supports a causative association between fluoroacetate accumulation and this adverse event.[5,6] 5-FU has not traditionally been dose-adjusted for patients with renal failure as the drug is primarily metabolized in the liver. Further studies regarding the risk of fluoroacetate accumulation could determine best practices in safely administering 5-FU to patients with renal failure.[6] Our patient became encephalopathic following her initial 5-FU administration with a dose of 4105 mg; however, she showed improvement within 2 days following discontinuation of the infusion. The immediate recovery supports the "5-FU catabolite type," where the catabolic pathways are still intact; however, it is the inadequate excretion of 5-FU catabolites and the administration of 5-FU that leads to the encephalopathy seen in our patient.[7] Our patient with CKD would have impaired elimination, which would allow the accumulation of 5-FU and fluoroacetate. This accumulation resulted in a transient encephalopathy that improved within 2 days following cessation of the chemotherapeutic drug.

Interestingly, there is a 3–15% rate of partial DPD deficiency and a 0.1–0.5% rate of complete DPD deficiency in the general population.[3] DPD breaks down 5-FU, so a deficiency in this enzyme increases the incidence of many 5-FU side effects related to its anabolic cytotoxic activity. One would expect that if hyperammonemia is related to the 5-FU catabolite fluoroacetate, DPD deficiency would be protective against this adverse effect. However, the accumulation of 5-FU caused by DPD deficiency can penetrate the cerebrospinal fluid and cause neuronal demyelination. Symptoms of encephalopathy as well as GI and marrow toxicity would appear among DPD deficiency patients immediately following the initial infusion of the chemotherapeutic drug. Remyelination would take weeks to months following the termination of 5-FU infusion.[7] Although there are insufficient data on the relationship between DPD activity and hyperammonemic encephalopathy, there are case reports of hyperammonemic encephalopathy occurring in patients with both partial and complete DPD deficiencies and in patients with elevated DPD activity suggesting that, further, research is needed in this area.[3,8,9] Once diagnosed, there are no clear guidelines for management of 5-FU-induced hyperammonemic encephalopathy. It is generally managed with 5-FU discontinuation and administration of ammonia-lowering therapies including lactulose, low-protein diet, renal replacement, and ammonium chelators.[3]

CONCLUSION

There are no current guidelines regarding whether patients can be rechallenged with 5-FU following the development of hyperammonemic encephalopathy. The largest cohort of patients with this adverse effect included 14 patients who were rechallenged either with a full or reduced dose, and eight of these patients experienced relapse at a full dose of 5-FU.[3] Further, inquiry is needed to determine best practices for rechallenge, along with physician awareness and close monitoring among patients receiving chemotherapy. For now, the current treatment for patients diagnosed with 5-FU induced encephalopathy is discontinuing the infusion.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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