Hepatobiliary Hyperammonemic Encephalopathy Associated With Fibrolamellar Hepatocellular Carcinoma: Case Report, Literature Review, and Proposed Treatment Algorithm

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Abstract

We report a case of a 31-year-old man with metastatic fibrolamellar hepatocellular carcinoma (FLHCC) treated with gemcitabine and oxaliplatin complicated by hyperammonemic encephalopathy biochemically consistent with acquired ornithine transcarbamylase deficiency. Awareness of FLHCC-associated hyperammonemic encephalopathy and a pathophysiology-based management approach can optimize patient outcome and prevent serious complications. A discussion of the management, literature review, and proposed treatment algorithm of this rare metabolic complication are presented. The Oncologist 2016; 21:514–520

Implications for Practice: Pathophysiology-guided management of cancer-associated hyperammonemic encephalopathy can improve patient outcome and prevent life-threatening complications. Community and academic oncologists should be aware of this serious metabolic complication of cancer and be familiar with its management.

Introduction

Fibrolamellar hepatocellular carcinoma (FLHCC) is a distinct form of primary liver cancer with respect to its epidemiology, cause, prognosis, and distinctive genomic profile. It affects adolescents and young adults without pre-existing liver disease or cirrhosis [1, 2]. This rare tumor represents approximately 5% of all hepatocellular carcinomas (HCCs), but the exact numbers vary between 0.6% and 9% in different studies [2–5].

Currently, surgical resection remains the front-line treatment for FLHCC, providing the only opportunity for potential cure. Nonetheless, survival is jeopardized by tumor recurrence and metastases. Unfortunately, for patients with unresectable or metastatic disease, treatment options are limited [6]. Clinical experience with cytotoxic chemotherapy has not demonstrated substantial activity in FLHCC, and no standard treatment of this rare malignancy has been established [5]. Furthermore, progress in the treatment of advanced FLHCC has been halted by the lack of dedicated clinical trials due to small numbers of patients and lack of funding support. According to anecdotal experience, many chemotherapeutic agents have been used in FLHCC, including fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan. Pediatric patients have tended to be treated according to a hepatoblastoma paradigm using various combinations of cisplatin, doxorubicin, ifosfamide, vincristine, cyclophosphamide, etoposide, and fluoropyrimidines [7]. A phase II HCC study including nine patients with FLHCC observed a complete response in one patient and a partial response in four patients with use of a 5-fluorouracil–interferon combination [8]. No effective targeted therapies have been described, however.

Hyperammonemia (HAE) has been described in association with a variety of tumors, including typical and fibrolamellar HCC, neuroendocrine tumors, gastrointestinal stromal tumors (GIST), and myeloma [9–12]. We present a case report of a severe HAE in a patient treated for HCC and propose a diagnosis and treatment algorithm of HAE in fibrolamellar HCC.

Case Report

A 31-year-old man presented with a history of 20 pounds of unintentional weight loss over 6 months, abdominal bloating, and hepatomegaly. Computed tomography (CT) demonstrated...
a large hepatic mass involving both lobes with areas of necrosis. Biopsy showed FLHCC (Fig. 1). Magnetic resonance imaging of the liver confirmed a large heterogeneous mass encompassing both lobes of the liver, measuring 23.8 cm in maximal dimension; peritoneal implants were seen in the left abdomen, measuring up to 8.3 cm in maximal dimension. Initial laboratory assessment demonstrated normal bilirubin, slightly elevated aminotransferase levels (aspartate aminotransferase [AST], 87 U/L; alanine aminotransferase [ALT], 86 U/L), normal alkaline phosphatase, \( \alpha \)-fetoprotein (AFP) of 77.1 ng/mL, and negative results on hepatitis B and C serologic testing.

Given the extent of the tumor and the presence of extrahepatic disease, the patient was not considered to be a candidate for resection. Systemic treatment was initiated with gemcitabine, 1,000 mg/m\(^2\), and oxaliplatin, 100 mg/m\(^2\) (GEMOX), every 2 weeks. On day 3 after receiving his first dose of GEMOX, the patient presented with mental status change, somnolence, and tremor, prompting admission. Further investigation revealed an ammonia level of 300 \( \mu \)mol/L and \( \alpha \)-fetoprotein (AFP) of 77.1 ng/mL, suggesting a paraneoplastic cause of his metabolic disorder (Fig. 2).

Follow-Up
GEMOX was continued despite the episodes of HAE during the first two cycles because of the significant clinical benefit. The patient’s cancer-related symptoms resolved, and AFP declined from 77 to 14 ng/mL. Restaging CT of the abdomen after six cycles GEMOX showed overall stable disease but no reduction in tumor size.

After introduction of sodium benzoate and citrulline, a dietary plan, and outpatient intravenous dextrose infusion on days 2–5 of chemotherapy, our patient was able to regain a near-normal quality of life, allowing the family much-needed time and giving the patient the ability to make his own treatment-related decisions. No further admission for encephalopathy occurred after cycle 3 of GEMOX chemotherapy. The patient developed a severe hypersensitivity reaction to oxaliplatin during his cycle 8 infusion, and GEMOX was discontinued. Even after a 4-week chemotherapy break, the patient’s ammonia level remained elevated (up to 127 \( \mu \)mol/L), suggesting a paraneoplastic cause of his metabolic disorder (Fig. 2).
In an attempt to identify potentially actionable therapeutic targets, a comprehensive next-generation sequencing assay was performed. However, this testing revealed no genomic alterations in the \(c\)-MET, mitogen-activated protein kinase/extracellular signal-regulated kinase, Akt-mammalian target of rapamycin, or ErbB signaling pathways and no mutations in \(EGFR\), \(BRCA\), or \(KRAS\) genes. DNAJB1-PRKACA fusion was present. Given limited treatment options and after multidisciplinary reevaluation, a decision was made to proceed with salvage debulking surgery. The patient underwent extended left hepatectomy, omentectomy, and extensive lymph node dissection. His ammonia level was monitored peri- and intraoperatively according to the protocol designed by the metabolic team. During the 9-hour surgery, the patient’s serum ammonia level did not exceed 40 \(\mu\)mol/L. Since tumor removal, the ammonia level has remained within normal limits. Sodium benzoate and citrulline were discontinued. The patient resumed a regular diet. Plasma amino acids panel 1 month after surgery were normal.

**DISCUSSION**

HAE is a rare, potentially life-threatening metabolic condition that can be associated with cancer or its treatment. HAE can be related to cancer itself as a result of ammonia production by the tumor, the tumor’s elevated requirement for amino acids, a portosystemic or intrahepatic shunt, or a combination of these mechanisms [9, 13].

Initially described 30 years ago, chemotherapy-related HAE has been reported mostly in patients with hematologic malignancies undergoing intensive cytoreductive treatment or bone marrow transplantation [14–16]. Several case reports and small case series described development of HAE in patients treated with a variety of agents, including conventional cytotoxics, such as 5-fluorouracil, \(L\)-asparaginase, cytarabine, cyclophosphamide, oxaliplatin, vincristine, etc.
etoposide, anthracyclines, busulfan, methotrexate, topotecan, vinorelbine, and gemcitabine [16–19]. Steroids, commonly used for premedication or as part of chemotherapeutic regimens, can contribute to the development of HAE [20–22]. HAE has been reported with novel and more recently approved agents, such as tyrosine kinase inhibitors (TKIs), including sunitinib, sorafenib, and regorafenib [19, 23, 24]. There is no established management algorithm for cancer- or chemotherapy-related HAE. Thus, a treatment approach to this metabolic phenomenon is extrapolated from principles of management of hepatic hyperammonemic encephalopathy or urea cycles disorders.

Intriguingly enough, despite the rarity of FLHCC, several other cases of life-threatening HAE were described in FLHCC patients, either at presentation or triggered by systemic chemotherapy [12, 14, 25–28]. Proposed mechanisms of HAE in FLHCC patients remain the same as in other tumor types, including additional insult induced by chemotherapy, resulting in increased cell breakdown and nitrogen load; an overwhelming urea cycle, as seen with congenital enzymatic deficiencies; and aggravation of pre-existing hyperammonemia [25, 27]. In addition, decreased OTC expression and inhibition by cancer itself can play a role [8].

The metabolic profile of our patient was highly suggestive of OTC deficiency, but he does not have a germline alteration in the OTC gene. Therefore, we believe our patient developed an acquired form of OTC deficiency associated with his malignancy, which was further aggravated by GEMOX chemotherapy.

Our case echoes another case recently reported by Sulaiman et al., in which ammonia levels remained elevated even when the patient was off chemotherapy [25]. This unusual association suggests a potential paraneoplastic syndrome associated with FLHCC. We can only hypothesize possible mechanisms contributing to this paraneoplastic syndrome. These include suppression of the OTC enzyme or increased utilization of arginine by the tumor for proliferation, leading to a deficiency of ornithine and consequently a deficiency of the substrate for the enzyme and decreased flux. Uregulation of glycolysis and suppression of the Krebs cycle were reported in FLHCC cells and might contribute to this paraneoplastic phenomenon [29].

Although this may be, to our knowledge, the first reported case of hyperammonemic encephalopathy due to acquired OTC deficiency in a patient with FLHCC treated with GEMOX, we do not think that this condition is specific to the chemotherapeutic regimen; rather, it is likely tumor-specific. Given potential neurological sequelae, awareness of this serious metabolic phenomenon is essential. Timely diagnosis and pathophysiology-guided treatment can prevent not only serious neurological complications, such as brain edema, seizures, and permanent neurological damage, but also allow continuation of potentially life-saving cancer treatment. Because the sutures of the skull in adults are fused, sensitivity to hyperammonemia-related cerebral edema appears considerably greater in adults than in children [30]. Thus, treatment should be aggressive and timely.

Diagnosis and Treatment Algorithm

There is no established management protocol for HAE in cancer and chemotherapy patients. Because of the rarity of HAE in this subset of patients, management recommendations are extrapolated from those for inherited urea cycle disorders, and anecdotal case reports data are available for guidance [28, 30–32]. Herein, we propose an algorithm for the diagnosis and management for FLHCC-related hyperammonemic encephalopathy (Fig. 3A, 3B).

Screening and Diagnosis

All patients with a new diagnosis of FLHCC should have baseline ammonia levels checked, regardless of liver function. Patients and caregivers should be educated about the signs, symptoms, and possible triggers of the condition. In patients with encephalopathy, the ammonia level should be part of the initial testing panel. If ammonia level is elevated, further testing for urea cycle disorders should be considered, including quantitative plasma and urinary amino acid, urinary organic acids, and orotic acid analyses. Molecular analysis can be used to rule out pre-existing inborn errors of the urea cycle, but enzymatic assays for OTC require hepatic tissue.

Treatment

Treatment of hyperammonemia must be initiated in a timely manner and should begin even before confirmation of the underlying cause. Delays in treatment and failure to maximize appropriate treatment may lead to permanent neurological damage and impair the patient’s ability to undergo life-saving treatment. Treatment of hyperammonemia should focus on management of an acute episode and prevention of further episodes. It is directed toward (a) reducing the nitrogen load in the system, (b) removing excess ammonia, and (c) correcting precipitating causes. Consultation and transfer of patient to a tertiary center with a metabolic service equipped with dealing with hyperammonemia may be required.

In acute management of HAE, intravenous fluids with 10%–20% dextrose and electrolytes should be started to mitigate catabolism and dehydration. The goal is to support a calorie intake of approximately 1.5 times the basal requirement; in adults, 6–8 mg/kg per min of glucose (mL/kg per day of 10% glucose) or 60 kcal/kg per day. If hyperglycemia (glucose > 150 mg/dL) occurs with 10%–20% dextrose, insulin should be started. Intralipids may need to be provided to meet the calorie requirement. The nitrogen load is further reduced by removal of protein from oral or intravenous intake for 24–48 hours.

Intravenous ammonia scavenger therapy with sodium benzoate and sodium phenylacetate (Ammonul; Valeant Pharmaceuticals North America LLC, Bridgewater NJ, http://www.valeant.com), routinely used in patients with congenital urea cycle defects, should be started if ammonia levels are greater than 100 µM (and confirmed on a repeat specimen). Sodium benzoate conjugates and sodium phenylacetate are also effective in the management of encephalopathy in cancer-related hyperammonemia. The nitrogen-scavenging drugs are usually administered in a large volume of fluid, which should be considered. Because these patients have cerebral edema, care should be taken to avoid overhydration. As a result of the complexity of administering ammonia scavenger drugs, consultation with an experienced metabolic physician is recommended before starting treatment [30].

If ammonia levels between 250 and 500 µM fail to respond to the high-calorie infusion plus ammonia scavenger therapy, additional treatment with sodium benzoate and sodium phenylacetate can be considered. If ammonia levels persist above 500 µM, additional treatment with sodium benzoate, sodium phenylacetate, and sodium benzoate conjugates can be administered.


diagram
scavenger therapy within 4–6 hours, or if the ammonia level exceeds 500 μM, dialysis/rapid hemofiltration should be started immediately at the highest available flow rate. Dialysis should also be considered when ammonia levels reach 250–500 μM if ammonia scavenger therapy is not available. Dialysis is effective for the removal of ammonia, either via intermittent hemodialysis or continuous arteriovenous or venovenous hemofiltration. Plasma ammonia levels usually fall sharply, and dialysis may be stopped after levels fall below 200 μmol/L. Hemodialysis provides the highest ammonia extraction, but some patients experience acute relapses after its discontinuation. Parenteral or enteral supplementation with arginine can increase the rate of urea production and nitrogen clearance and replenish this essential amino acid.

Drugs that decrease nitrogen reabsorption from the gut or production in the intestine can be used in the treatment of HAE on the basis of clinical observations, easy availability, and clinician familiarity with these agents. The dosing and schedule are purely extrapolations from guidelines for the treatment of hepatic encephalopathy in chronic liver disease. Nonabsorbable disaccharide lactulose is the first choice for treatment of episodic overt hepatic encephalopathy; however, the role of lactulose in the treatment of HAE related to cancer or chemotherapy is not well established. It can be used along with other HAE treatment steps or when ammonia

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**Figure 3.** Screening and diagnosis (A) and management of acute episodes (B) of hyperammonemia.

Abbreviations: FLHCC, fibrolamellar hepatocellular carcinoma; IV, intravenous; PEG, percutaneous endoscopic gastrostomy; PO, oral.
scavenging therapy is not available. During acute episodes, lactulose can be administered via nasogastric tube or enema in patients who are unable to swallow or have an aspiration risk. There is danger of overuse of lactulose, however, leading to complications such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation, and overuse can precipitate HAE. Gastrointestinal side effects of lactulose can interfere with patients’ quality of life.

The role of rifaximin is even less clear in cancer-related HAE. Given the cost of rifaximin and its unclear benefit, we suggest the use of treatment based on the pathogenesis of HAE, such as ammonia scavenger drugs when available [33, 34].

A final step is to screen for and treat precipitating or contributing factors. These factors include infections, electrolyte imbalance, hypokalemia, and metabolic alkalosis and hypovolemia.

Prevention

Once the acute crisis has passed and hyperammonemia improves, the use of ammonia scavengers should be continued during chemotherapy and switched to the oral formulation if feasible. Repletion of arginine should continue in patients with decreased activity of a urea cycle enzyme. Repletion of arginine should continue in patients with decreased activity of a urea cycle enzyme. An episode of HAE suggests an increased risk for recurrent HAE and may change in chemotherapeutic regimen, anesthesia, surgery, or liver-directed therapy. It is imperative to prevent or quickly interrupt a catabolic state at an early stage of impending decompensation during subsequent illnesses or surgeries.

Diet remains one of the mainstays in the prevention of HAE in urea cycle disorders [35]. Protein is gradually reintroduced 24–48 hours after an acute hyperammonemic crisis. In situations where hyperammonemia is anticipated after a trigger, such as the chemotherapy in our patient, the protein intake should be reduced to half of baseline for a day before and after the anticipated peak of hyperammonemia. Calorie intake should be maximized with carbohydrate and fat intake. It may be necessary to replace some intact proteins with essential amino acids to achieve the minimal protein need while reducing the nitrogen load. Consultation with a nutritionist familiar with urea cycle disorders is advisable.

Conclusion

We described the presentation, treatment, and proposed management algorithm of hyperammonemic encephalopathy due to acquired OTC deficiency in a patient with FLHCC treated with gemcitabine and oxaliplatin. Prompt diagnosis and pathophysiology-guided management of life-threatening hyperammonemia allowed the continuation of life-saving chemotherapy in an otherwise healthy young patient with a rare liver tumor. We believe that patients with FLHCC have a particular predilection for hyperammonemic encephalopathy due to the tumor itself or its treatment.

Clinicians should be aware about this serious metabolic complication of FLHCC and be familiar with its management. Clinical trials with novel TKIs (ClinicalTrials.gov Identifier: NCT02234986) and immunotherapy in this rare disease have started or are likely to be launched. The potential effect of these new agents on urea cycle should be cautiously examined. The diagnostic and treatment algorithm described here can be partially applied to HAE related to any malignancies, regardless of chemotherapeutic agent or trigger.

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Disclosures

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