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Surgical Debulking for Refractory Hyperammonemic Encephalopathy in Fibrolamellar Hepatocellular Carcinoma

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Fibrolamellar hepatocellular carcinoma (FLC) is a rare form of liver cancer that usually affects children and young adults without underlying cirrhosis. Hyperammonemic encephalopathy (HAE) has been reported in patients with FLC, but the pathogenesis and optimal management of hyperammonemia (HA) in FLC are unclear. We report on two cases of HAE in patients with FLC and preserved liver function. The successful management of HA with surgical debulking of FLC tumors is described.

Case 1

A 26-year-old male with a 2-year history of FLC developed progressive somnolence and disorientation. Treatment history for FLC had included cytotoxic chemotherapy, lenvatinib, and immunotherapy. A CT scan confirmed extensive-stage FLC with numerous liver, lung, and pelvic metastasis. Laboratory results showed bilirubin 0.3 mg/dL, creatinine 0.4 mg/dL, leukocytes of $9.5 \times 10^9/L$, hemoglobin 11.2 g/dL, platelets $369 \times 10^9/L$, and ammonia 247 $\mu\text{mol/L}$ (reference range, 0–32). Plasma amino acid analysis revealed relatively low citrulline (14 $\mu\text{mol/L}$), arginine (32 $\mu\text{mol/L}$), and ornithine (35 $\mu\text{mol/L}$). Urinary orotic acid excretion was markedly elevated at 149 mmol/mol creat (reference range, 0.68–3.52).

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Potential conflict of interest: Nothing to report.

Informed Consent

Informed consent was obtained from the patients.

The patient was treated with i.v. sodium benzoate and sodium phenylacetate, arginine hydrochloride, and dextrose 10% (D10) 0.45% normal saline. He was transitioned to oral glycerol phenylbutyrate, but developed worsening HA over time. Approximately 6 weeks later, he underwent an extensive debulking surgery as a treatment for refractory HA in the setting of advanced FLC, including resection of the descending colon and *en bloc* resection of retroperitoneal nodules and pelvic masses, collectively removing ~50% of the tumor volume. The patient's ammonia levels significantly improved (Fig. 1), and his lethargy and disorientation resolved.

Case 2

A 25-year-old male with a recent diagnosis of FLC ~1 month earlier presented to the emergency room after his mother found him unarousable in bed. He was intubated upon arrival for airway protection. He had two previous hospital admissions for HAE over the preceding 3 weeks. He was receiving outpatient treatment for his FLC with gemcitabine plus oxaliplatin.

Laboratory results showed bilirubin 0.3 mg/dL, creatinine 1.17 mg/dL, leukocytes of $9.5 \times 10^9/L$, hemoglobin 11.2 g/dL, platelets $369 \times 10^9/L$, and ammonia 347 $\mu\text{mol/L}$. Plasma amino acid analysis revealed low citrulline (0 $\mu\text{mol/L}$), arginine (30 $\mu\text{mol/L}$), and ornithine (20 $\mu\text{mol/L}$). He received i.v. sodium benzoate and sodium phenylacetate, as well as arginine hydrochloride. However, his refractory HA required concurrent treatment with continuous venovenous hemofiltration (CVVH) and rebounded rapidly if either CVVH or i.v. nitrogen scavenging was discontinued. It was determined that the patient was unlikely to be safely discharged unless a more definitive solution for his HA could be established. A CT scan revealed a 9-cm lesion in the left liver and diffuse peritoneal metastatic disease. The patient was offered a palliative debulking surgery for his cancer, including left hepatectomy and omentectomy, with an estimated removal of 50% of his total tumor volume. After surgery, he was successfully transitioned to oral glycerol phenylbutyrate and L-citrulline with ammonias of 80–100 $\mu\text{mol/L}$ as an outpatient.

Discussion

HAE has been reported in patients with FLC.⁽¹⁾ FLC generally occurs in young patients with preserved liver function, and previous cases of FLC-associated HAE have not been linked to hepatic impairment. Portosystemic shunting or anatomical compression of the liver vasculature resulting in impaired nitrogen clearance is a potential mechanism for HA⁽¹⁾; however, the degree of HA in these cases was out of proportion to the degree of shunting. In both cases, HA improved with surgical tumor debulking, supporting a direct link between FLC and HA. Although the threshold of tumor reduction necessary to ameliorate HA in FLC is unknown, ~50% tumor reduction was sufficient in both cases and may be a reasonable goal for surgical debulking. It has been proposed that FLC may result in HA through consumption of ornithine for polyamine synthesis, which reduces the availability of ornithine for the proximal urea cycle.⁽²⁾ The striking orotic aciduria and low citrulline in our patients, and the response to surgical tumor debulking, supports this mechanism. Our proposed management of FLC-associated HA (Table 1) draws from experience in managing

ornithine transcarbamylase deficiency. Pharmacological treatment of HA using nitrogen scavengers, and more definitive options focusing on decreasing the tumor volume, including tumor debulking surgery, should be considered in these patients. Further exploration into the pathophysiology and treatment of HA in FLC is necessary to refine treatment approaches.

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Abbreviations:

CVVH	continuous venovenous hemofiltration
FLC	fibrolamellar cancer
HA	hyperammonemia
HAE	hyperammonemic encephalopathy

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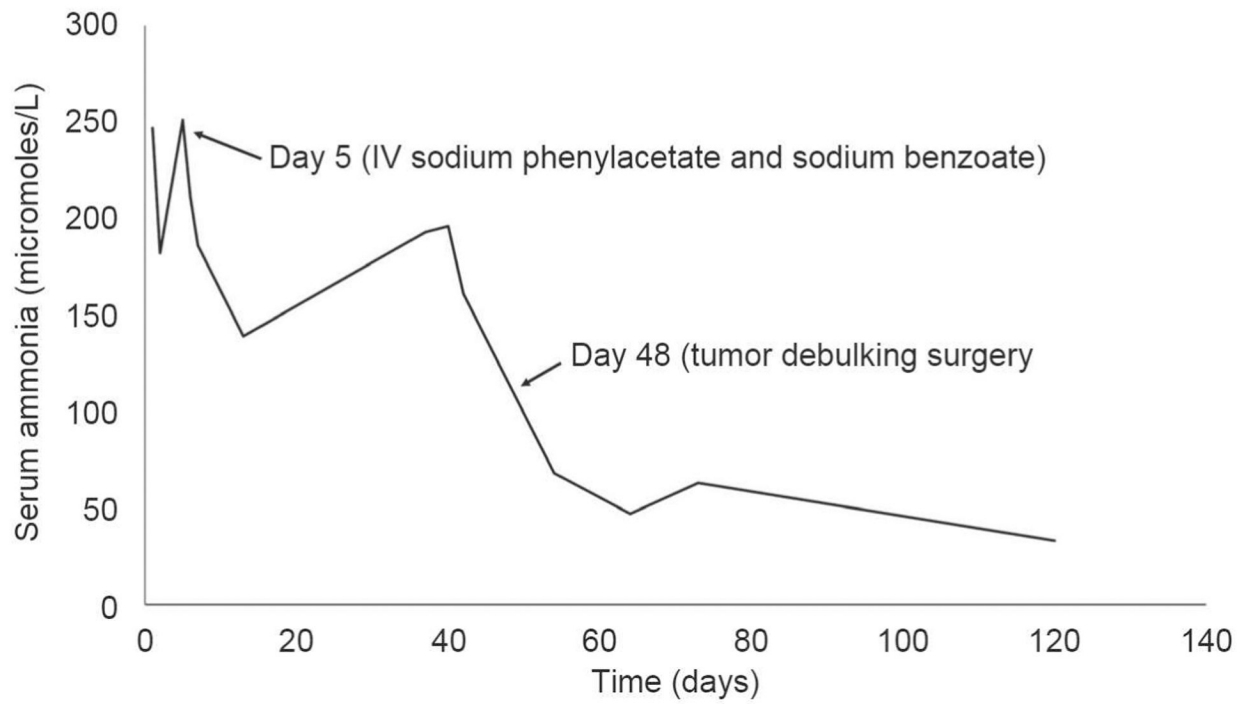


FIG. 1.
Trend in ammonia levels over time.

TABLE 1.

Suggested Management of HA in FLC

Management Options	Commonly Used Measures
Outpatient management	Oral nitrogen scavenger (e.g., sodium phenylbutyrate, glycerol phenylbutyrate) and L-citrulline
Emergent cases	CVVH; i.v. sodium benzoate and sodium phenylacetate, arginine hydrochloride, and D10-based fluids
Refractory to medical therapy	Consideration of debulking surgery to reduce FLC tumor volume, in conjunction with medical management, when feasible, and consistent with the overall goals of care