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Refractory Hyperammonemic Encephalopathy as a Paraneoplastic Presentation of Fibrolamellar Hepatocellular Carcinoma: A Case Report

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Manuscript Preparation E
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Patient: Male, 24-year-old
Final Diagnosis: fibrolamellar hepatocellular carcinoma • hyperammonemic encephalopathy
Symptoms: Altered mental status • confusion
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology • General and Internal Medicine • Oncology

Objective: Rare disease

Background: Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare liver malignancy affecting adolescents and young adults without underlying liver disease. Hyperammonemic encephalopathy (HAE) is an uncommon but severe complication in advanced FLHCC, resulting from progressive hepatic dysfunction or tumor-related metabolic derangements. Early recognition is essential to prevent neurologic decline and improve outcomes.

Case Report: A 24-year-old man with metastatic FLHCC presented with worsening confusion for 1 month. His prior treatments included transarterial radioembolization, multiple resection surgeries, and multiple chemotherapies. On examination, he was oriented only to self and had asterixis. Laboratory evaluation showed severe hyperammonemia (251 µmol/L), suggesting HAE. MRI brain was unremarkable, and EEG showed moderate encephalopathy. Plasma amino acid analysis showed marked depletion of urea cycle intermediates (citrulline, arginine, ornithine) with low alanine and glutamine, and elevated urinary orotic acid, which suggests impaired ornithine transcarbamylase activity and an acquired urea cycle disorder. Treatment was initiated with rifaximin and lactulose initially, followed by ammonia scavenger therapy of sodium benzoate–sodium phenylacetate. Despite this treatment, ammonia levels remained elevated, prompting hemodialysis and continuous renal replacement therapy. However, he continued to deteriorate and eventually died of his illness.

Conclusions: HAE is a rare paraneoplastic manifestation of FLHCC. Conventional therapies for cirrhosis-related encephalopathy, such as lactulose and rifaximin, are often ineffective. Management instead relies on ammonia-scavenging agents and arginine supplementation, with renal replacement therapies reserved for refractory cases. Outcomes remain poor when encephalopathy persists despite dialysis, underscoring the need for multidisciplinary management and early integration of palliative care.

Keywords: Fibrolamellar Hepatocellular Carcinoma • Hyperammonemia • Hyperammonemic Encephalopathy • Paraneoplastic Syndromes • Urea Cycle Disorders

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/952819

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Introduction

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare, distinct variant of hepatocellular carcinoma (HCC). It represents 5% of all HCCs, with an age-adjusted incidence rate of 0.02 per 100 000 individuals [1,2]. It was first described by Edmondson in 1956, who studied an adult-type liver tumor in a 14-year-old adolescent girl without any preexisting liver disease [3]. However, it was not until 1980 that the term FLHCC was coined by Craig et al, who described the clinical and pathological features of FLHCC in a series of 23 patients [4]. Furthermore, the World Health Organization (WHO) Classification of Tumors recognized this variant of HCC as a distinct entity and designated a WHO classification number as recently as 2010 [5].

FLHCC is distinct from HCC in that it primarily affects adolescents and young adults between 10 and 35 years of age without underlying chronic liver disease like viral hepatitis, fibrosis, or cirrhosis; in comparison, the average age at presentation in patients with HCC is 65 years [1,2,6]. FLHCC patients are more likely to be females (51.5% versus 26.3%) and White (85.3% versus 56.9%) compared with HCC patients.[2] The clinical presentation of FLHCC is variable and can include abdominal pain, pain at sites of metastasis, a palpable abdominal mass, or abdominal distention due to ascites [7]. In rare cases, FLHCC patients presents with altered mental status due to hyperammonemic encephalopathy (HAE) and acquired urea cycle defect.

Honeyman et al first described a distinct pathogenic mechanism of recurrent DNAJB1–PRKACA fusion transcripts arising from a ~400-kilobase deletion on chromosome 19 in FLHCC, which differentiates it from conventional HCC and cholangiocarcinoma [8]. This fusion transcript produces an active chimeric kinase that drives the growth of tumor cells. On histopathology, FLHCC is characterized by large polygonal neoplastic hepatocytes with abundant eosinophilic cytoplasm due to numerous mitochondria, prominent nuclei, and strands of collagen fibers arranged in a lamellar fashion [9].

Localized FLHCC is potentially curable with surgical resection, with a 5-year overall survival estimated at 52% to 62% after surgery [10]. However, in cases of unresectable, metastatic, or recurrent disease, treatment options are limited and largely anecdotal due to the rarity of the tumor. Chemotherapeutic agents such as fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan have shown limited efficacy in the treatment of FLHCC. Prognosis in case of advanced disease is poor, with a 5-year overall survival of less than 10% to 20% [7].

In this study, we report a unique presentation of FLHCC with paraneoplastic HAE that was refractory to treatment with ammonia-scavenging medications and hemodialysis.

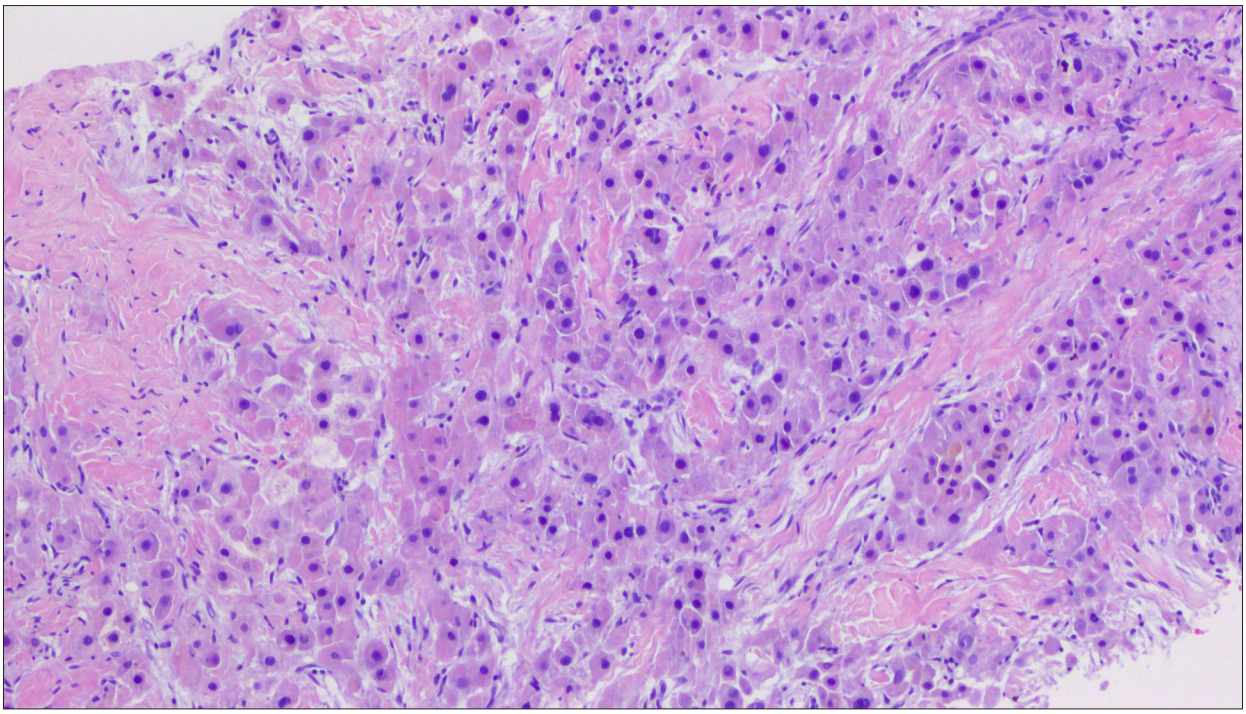

Figure 1. Biopsy from liver mass showing large pleomorphic neoplastic polygonal cells with abundant eosinophilic cytoplasm, nuclear inclusions, and prominent nucleoli arranged in nests and sheets, separated by collagenous fibrous bands characteristic of fibrolamellar hepatocellular carcinoma.

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Table 1. Laboratory parameters at admission.

Parameter	Result	Normal range
WBC (×10³/μL)	7.21	4.0-11.0
HGB (g/dL)	11.5	13.5-17.5 (male) / 12.0-15.5 (female)
PLT (×10³/μL)	520	150-450
Prothrombin time (seconds)	16.3	11.8-14.8
INR	1.3	0.9-1.1
Serum sodium (mmol/L)	136	135-145
Serum potassium (mmol/L)	4.1	3.5-5.1
Bicarbonate (mmol/L)	20	22-30
Glucose serum (mg/dL)	109	74-106
BUN serum (mg/dL)	6.9	9-20
Creatinine (mg/dL)	0.34	0.66-1.25
Serum calcium (mg/dL)	8.2	8.4-10.2
Serum albumin (g/dL)	2.9	3.5-5.0
Serum protein (g/dL)	5.0	6.3-8.2
Total bilirubin (mg/dL)	0.6	0.2-1.2
AST (IU/L)	145	10-50
ALT (IU/L)	184	10-50
Alkaline phosphatase (IU/L)	185	55-149
Serum ammonia (μmol/L)	271	0-35
CRP (mg/dL)	70.5	0-1.0
Lactic acid (mmol/L)	1.7	0.7-2.1
Urine orotic acid (mmol/mol)	9	0-2
Hepatitis B surface antigen	Non-reactive	
Hepatitis B core antibody	Negative	
Hepatitis A, IgM	Negative	
Anti-hepatitis C antibody	Non-reactive	

Abbreviations: WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count; BUN, blood urea nitrogen; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Case Report

A 24-year-old man with a past medical history of metastatic FLHCC (with intra-abdominal and intrathoracic metastases) presented to our facility with worsening confusion for 1 month. He concurrently endorsed a significant unintentional weight loss of 14 kg over 5 months. His past medical history included a diagnosis of FLHCC at 17 years of age, with liver mass biopsy showing large pleomorphic neoplastic polygonal cells with abundant eosinophilic cytoplasm, nuclear inclusions, prominent nucleoli arranged in nests and sheets, and collagenous fibrous bands, which is diagnostic of the fibrolamellar variant of hepatocellular carcinoma (**Figure 1**). Fluorescence in situ hybridization for PRKACA rearrangement was positive, showing a rearrangement involving the PRKACA gene region (at 19p13.2) with loss of the 5'PRKACA probe and retention of the 3'PRKACA probe, correlating with the DNAJB1-PRKACA fusion event classically associated with fibrolamellar carcinoma. At the time of diagnosis, the patient's tumor was deemed unresectable. Hence, he was treated with 2 sessions of trans arterial radioembolization with Yttrium-90 in the left hepatic artery, Nivolumab (discontinued due to tumor progression),

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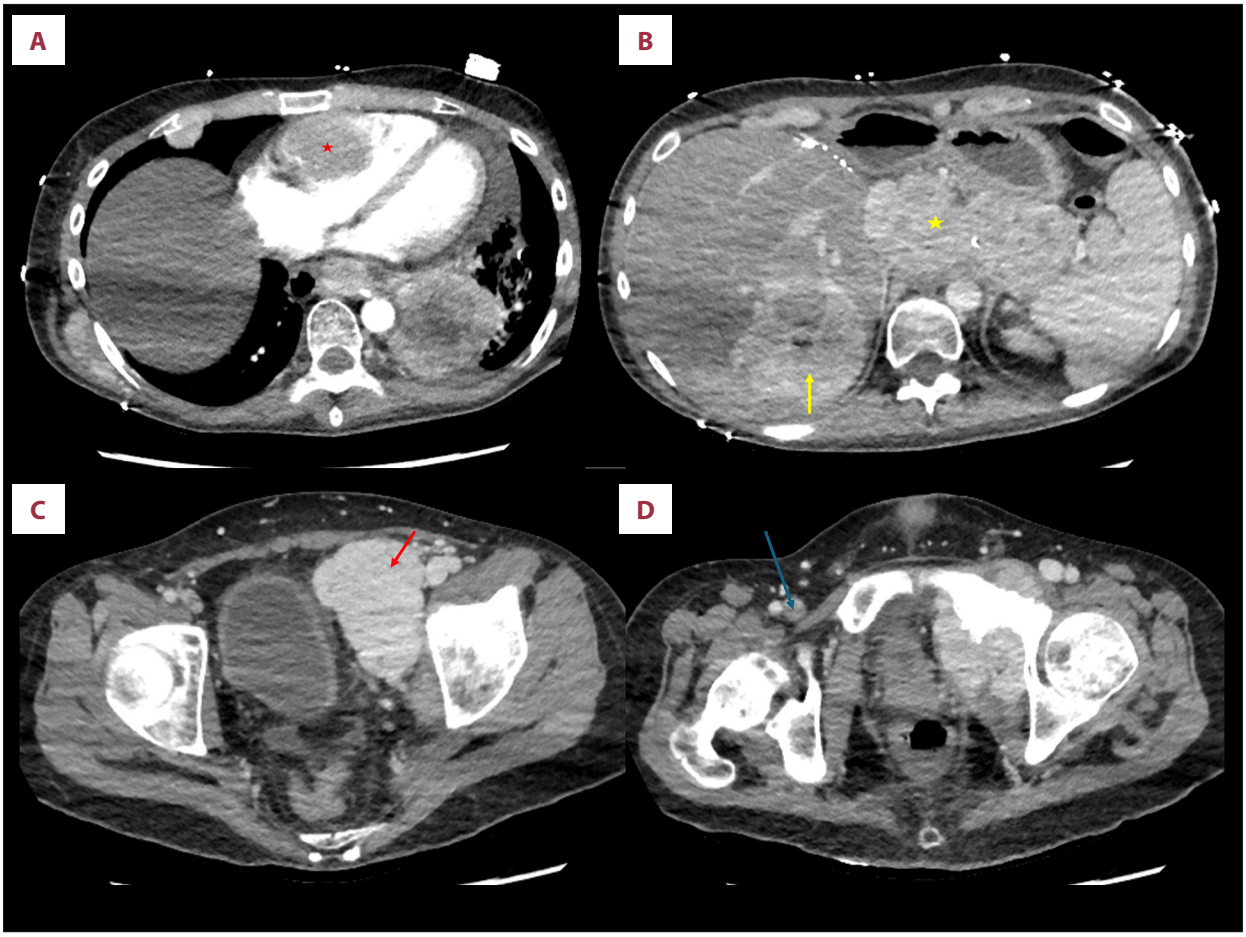

Figure 2. Contrast-enhanced computed tomography (CT) demonstrates widespread metastatic disease and thrombotic complications. Axial CT images show (**A**) a large intracardiac mass within the right ventricle (red star); (**B**) a 7.6 × 7.9 cm hepatic mass (yellow arrow) with additional intraperitoneal tumor deposits (yellow star); (**C**) a pelvic mass (red arrow); and (**D**) deep vein thrombosis in the right common femoral vein (blue arrow).

and cabozantinib before he underwent partial hepatectomy of the left lobe of the liver. Afterward, despite treatment, his cancer continued to progress with metastasis to the thoracic and intrabdominal lymph nodes, lung parenchyma, pancreas, spleen, and omentum. He received multiple salvage debulking surgeries. He was also treated with lenvatinib (held due to rash), regorafenib (held due to adverse effects), 4 cycles of the GEMOX regimen (gemcitabine and oxaliplatin), 2 cycles of pembrolizumab and ipilimumab (discontinued due to suspected grade IV autoimmune hepatitis), capecitabine, and radiation therapy to the abdominal lymph nodes and lung. He had a family history of breast cancer in his maternal grandmother. He denied any history of tobacco use, alcohol use, or recreational drug use. At presentation, he was afebrile, normotensive (blood pressure 124/73 mm Hg), and tachycardic (heart rate 133/min), with a normal respiratory rate and an appropriate oxygen saturation on ambient air. On physical examination, he was cachectic, had a percutaneous gastrostomy tube, was oriented only to person, and demonstrated asterixis (grade 2 encephalopathy). The remainder of the physical examination, including the neurological examination, was normal despite the limitations imposed by his altered mental status. Laboratory parameters at admission are shown in **Table 1**. On admission, his liver disease severity was classified as Child–Pugh Class B (score 7 points) with a MELD-Na score of 12 points.

The patient's serum ammonia level at presentation was 271 µmol/L. A computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain were normal. CT angiography of the chest and CT of the abdomen with intravenous contrast showed extensive metastatic disease, including large, bulky masses throughout the chest, mediastinum and chest wall, a large cardiac mass in the right ventricle, several intraperitoneal tumors, liver lesions and pelvic lesions, and a deep venous thrombosis in the right common femoral vein (**Figure 2**). The electroencephalogram showed diffuse background slowing, consisting of delta waves with an admixture of theta frequency, suggesting a moderate degree of

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Table 2. Plasma amino acid levels.

Plasma amino acid	Result (µmol/L)	Reference range (µmol/L)	Flag
Aspartic acid	3	1-4	Normal
Glutamic acid	55	10-97	Normal
Hydroxyproline	< 1	4-27	Low
Serine	71	65-138	Normal
Asparagine	18	31-64	Low
Alpha-aminoadipic acid	< 1	≤ 2	Normal
Glycine	120	122-322	Low
Glutamine	299	428-747	Low
Sarcosine	2	≤ 4	Normal
Beta-Alanine	3	≤ 5	Normal
Taurine	26	31-102	Low
Histidine	36	60-109	Low
Citrulline	2	16-51	Low
Arginine	17	43-107	Low
Threonine	35	67-198	Low
Alanine	174	200-483	Low
1-Methylhistidine	25	≤ 47	Normal
Gama-Aminobutyric acid	< 1	≤ 3	Normal
3-Methylhistidine	2	2-9	Normal
Beta-Aminoisobutyric acid	< 2	≤ 3	Normal
Proline	97	104-383	Low
Ethanolamine	5	5-13	Normal
Alpha-Aminobutyric acid	12	7-32	Normal
Tyrosine	47	38-96	Normal
Valine	106	132-313	Low
Methionine	15	16-34	Low
Cystathionine	< 1	< 1	Normal
Isoleucine	50	34-98	Normal
Leucine	62	73-182	Low
Phenylalanine	29	40-74	Low
Tryptophan	22	40-91	Low
Ornithine	< 1	27-83	Low
Lysine	106	119-233	Low

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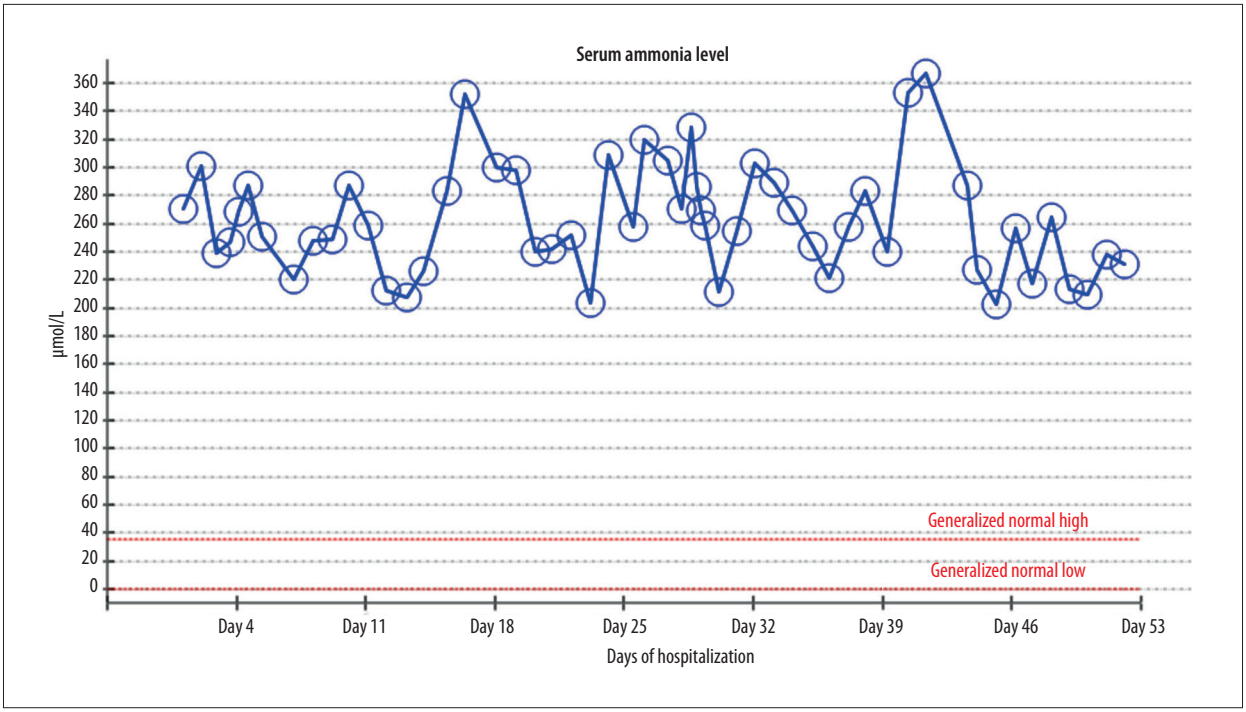

Figure 3. Trend of serum ammonia level over the course of hospitalization.

encephalopathy. The patient's plasma amino acids (**Table 2**) revealed low citrulline (2 µmol/L, normal: 16-51 µmol/L), low arginine (17 µmol/L, normal: 43-107 µmol/L), low ornithine (< 1 µmol/L, normal: 27-83 µmol/L), low alanine (174 µmol/L, normal: 200-483 µmol/L), and low glutamine (299 µmol/L, normal: 428-747 µmol/L) levels. His urinary orotic acid was elevated (9 mmol/mol, normal range, 0-2 mmol/mol of creatinine). This suggested a urea cycle disorder with impaired activity of the enzyme, ornithine transcarbamylase (OTC). OTC gene analysis and testing for enzymatic OTC activity was deferred due to logistical reasons.

Gastroenterology was consulted, and the patient was continued on lactulose and rifaximin 550 mg twice daily, with a target of 3 bowel movements per day. He was also started on nitrogen scavenger, sodium benzoate, and sodium phenylacetate (55 g/m^2) for 3 days to replenish urea cycle substrates. A high-calorie, low-protein diet was initiated. Due to a lack of improvement in serum ammonia level (251 µmol/L) with these treatments, Nephrology was consulted, and the patient was started on intermittent hemodialysis. Serum ammonia level (226 µmol/L) showed only mild reduction even after 5 sessions of intermittent hemodialysis. Hence, he was started on continuous renal replacement therapy (CRRT) with 2 consecutive days of 6-hour hemodialysis treatments. Still, serum ammonia levels remained refractory to treatment, and he continued to show signs of encephalopathy. Repeat treatment with sodium benzoate, sodium phenylacetate, and arginine (4 g/m^2, total of 7 g) was administered for 3 days, followed by 4 consecutive sessions of intermittent hemodialysis without any significant improvement in serum ammonia level. His mental status showed progressive decline, and he required intubation for airway protection. Repeat CT scan and MRI of the brain without contrast were unremarkable. Given his continued clinical deterioration and persistent elevation of serum ammonia level (**Figure 3**) despite all treatment, the Palliative team was consulted for goals of care transition to comfort care, and he died of his illness.

Discussion

Ammonia produced from protein metabolism is converted into urea by the liver through the urea cycle and excreted by the kidneys from the body. Failure of this physiologic pathway results in the accumulation of ammonia in the blood which crosses the blood-brain barrier and acts as a neurotoxin in the brain. This causes hyperammonemic encephalopathy (HAE). HAE presents as a spectrum of clinical manifestations of varying severity, including sleep-wake cycle changes, irritability, confusion, seizures, coma, and even death [11]. HAE is commonly seen in advanced liver failure, but it can also present as a rare, life-threatening complication of cancer or its associated treatment. Other rare causes of HAE include inherited metabolic defects of the urea cycle and organic acidemias [12]. HAE has been associated with malignancies like multiple myeloma, hepatocellular carcinoma, and following chemotherapy for hematologic malignancies and bone marrow transplantation [12-14]. However,

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Table 3. Summary of cases of fibrolamellar hepatocellular carcinoma with hyperammonemic encephalopathy, treatment, and outcomes.

No.	Paper	Age (years)	Sex	Timeline of HAE	Ammonia levels (µmol/L)	Treatment for FLHCC	Treatment for HAE	Outcome of FLHCC	Outcome of HAE
1	2008 Chan et al [31]	22	F	After 2 days of initiating chemotherapy	280	Chemotherapy (doxorubicin, cisplatin, fluorouracil, interferon-alfa)	Arginine, citrulline	Disease progressed	Improved
2	2009 Sethi et al [32]	18	M	Initial	137	Chemotherapy (sorafenib)	Not available	Died	Died
3	2012 Berger et al [33]	22	F	Initial	254	Not available	None	Not available	Not available
4	2012 Hashash et al [34]	18	F	Presented with HAE	342	Multiple resection surgeries	Mannitol, hyperventilation, therapeutic hypothermia, lactulose, rifaximin, and hemodialysis (ineffective); sodium phenylacetate and sodium benzoate (ineffective); then TPN with arginine supplementation	Remission	Improved
5	2014 Suliman et al [12]	20	F	6 years after diagnosis	410	Left hepatectomy and chemotherapy	IV sodium benzoate and phenylbutyrate infusion; oral sodium benzoate, phenylbutyrate, and arginine	Disease progressed	Improved
6	2015 Bender et al [35]	19	F	9 months after initial diagnosis	264	Chemotherapy (sorafenib, bevacizumab, erlotinib, platinum, doxorubicin, gemcitabine), surgery, and radiotherapy	Lactulose and rifaximin, sodium phenylbutyrate	Recurrence	Improved
7	2016 Alsina et al [36]	23	F	Initial	281	Chemotherapy (sorafenib) and liver transplantation	Sodium phenylbutyrate, sodium benzoate, arginine	Remission	Improved

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Table 3 continued. Summary of cases of fibrolamellar hepatocellular carcinoma with hyperammonemic encephalopathy, treatment, and outcomes.

No.	Paper	Age (years)	Sex	Timeline of HAE	Ammonia levels (µmol/L)	Treatment for FLHCC	Treatment for HAE	Outcome of FLHCC	Outcome of HAE
8	2016 Chapuy et al [1]	31	M	3 days after receiving chemotherapy	300	Chemotherapy (GEMOX × 6 cycles) and salvage debulking surgery	Lactulose (initial improvement); ammonia scavenger therapy with citrulline added for subsequent episodes	Stable disease	Improved
9	2017 Surjan et al [17]	31	M	1 week after diagnosis	312	Chemotherapy (sorafenib and GEMOX)	Neomycin, lactulose, and L-ornithine-L-aspartate; sodium benzoate and arginine	Not available	Improved
10	2018 Bartlett et al [37]	13	M	8 days after treatment	317	Chemotherapy (sorafenib, GEMOX, nivolumab, cyclophosphamide/ topotecan, crizotinib)	Arginine, lactulose, and rifaximin	Disease progressed	Improved
11	2018 Bartlett et al [37]	17	F	8th cycle of chemotherapy	329	Chemotherapy (sorafenib, GEMOX, cabozantinib, nivolumab)	Arginine and sodium benzoate/ sodium phenylacetate	Stable disease	Improved
12	2018 Suarez et al [38]	33	F	At diagnosis	Not ava-lable	Cadaveric liver transplantation	Hemofiltration and ammonium benzoate	No relapse	Improved
13	2019 Cho et al [6]	32	F	Not available	300	Chemoembolization, surgical resections, chemotherapy (nivolumab)	Sodium phenylacetate and benzoate	Not available	Improved within 2 days
14	2020 Thakral et al [39]	32	F	6 years after diagnosis	300	Chemoembolization, surgical resection, chemotherapy (sorafenib, ponatinib, GEMOX)	Lactulose, sodium phenylacetate, and arginine; L-citrulline, glycerol phenylbutyrate, lactulose, and rifaximin	Died	Died
15	2020 Lee et al [40]	18	M	At diagnosis of HCC	393	Chemotherapy (cisplatin, 5-fluorouracil, doxorubicin, interferon-alfa) and hemi-hepatectomy	Lactulose and rifaximin, then CVVH with sodium benzoate, sodium phenylacetate, arginine, carnitine, and 20% dextrose	Not available	Improved

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Table 3 continued. Summary of cases of fibrolamellar hepatocellular carcinoma with hyperammonemic encephalopathy, treatment, and outcomes.

No.	Paper	Age (years)	Sex	Timeline of HAE	Ammonia levels (μmol/L)	Treatment for FLHCC	Treatment for HAE	Outcome of FLHCC	Outcome of HAE
16	2020 Shah et al [41]	26	F	Not available	160	Surgical resection of liver, colon, and small bowel	Sodium benzoate and L-arginine	Not available	Improved
17	2020 Surjan et al [42]	39	F	8 years after diagnosis	663	Left hepatectomy with intrahepatic biliodigestive anastomosis	L-ornithine-L-aspartate, polyethylene glycol with lactulose, TPN with amino acid supplementation, hemodialysis, sodium benzoate	Not available	Improved
18	2022 Ahmed et al [15]	28	M	9 months after initial diagnosis	338	Chemotherapy (FOLFOX, atezolizumab/bevacizumab × 5 cycles, then GEMOX)	Lactulose, ammonia scavenger therapy	Disease progressed	Improved within 24 hours
19	Present case	24	M	7 years after diagnosis	271	TARE, multiple resection surgeries, chemotherapy (nivolumab, cabozantinib, lenvatinib, regorafenib, GEMOX, pembrolizumab/ipilimumab, capecitabine), and radiotherapy	Lactulose and rifaximin, then sodium benzoate–sodium phenylacetate and arginine, intermittent hemodialysis, and CRRT	Disease progressed	Died

F, female; M, male; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; FLHCC, fibrolamellar hepatocellular carcinoma; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GEMOX, gemcitabine and oxaliplatin; HAE, hyperammonemic encephalopathy; HCC, hepatocellular carcinoma; IV, intravenous; TARE, transarterial radioembolization; TPN, total parenteral nutrition.

HAE is an extremely rare paraneoplastic presentation of FLHCC, with only 18 cases described to date; we report the 19th case (**Table 3**) [15]. Various mechanisms have been proposed to explain the occurrence of HAE in FLHCC patients: (1) Excess nitrogen load production from increased tumor cell breakdown after chemotherapy; (2) A portosystemic or intrahepatic shunt; (3) Decreased expression of the Ornithine transcarbamylase (OTC) gene and enzyme by tumor cells, which is necessary for conversion of ammonia to urea; and (4) Excess consumption of arginine by the proliferating tumor cells, resulting in a deficiency of ornithine and decreased substrate availability to be used by the OTC enzyme in the urea cycle [1,6]. Different chemotherapeutic agents, including gemcitabine, oxaliplatin, and regorafenib, have been described to cause HAE, but our patient had not received any recent chemotherapy treatment to precipitate HAE [1,16]. Imaging of the abdomen was also not suggestive of any portosystemic shunt to explain the persistent hyperammonemia. The metabolic laboratory analysis, showing low plasma citrulline and arginine and elevated urine orotic acid, was highly suggestive of an acquired urea cycle enzymatic defect with OTC deficiency. We did not have the scope for molecular testing of the OTC gene, and a liver biopsy was

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not clinically indicated to assess OTC enzymatic activity. The likely explanation for this paraneoplastic phenomenon lies in its pathognomonic molecular hallmark: a DNAJB1-PRKACA fusion, seen in 80% of FLHCC patients, as seen in our patient [6]. This chimeric protein increases aurora kinase expression in tumor cells, thereby upregulating c-Myc transcription. c-Myc, in turn, leads to the overexpression of many genes involved in the carcinogenesis of FLHCC, including that of ornithine decarboxylase (ODC). ODC decarboxylates ornithine to participate in polyamine synthesis, which is essential for cellular growth. This imbalance between OTC and ODC leads to ornithine consumption and urea cycle disruption, resulting in hyperammonemia and encephalopathy [17]. Additionally, ammonia homeostasis is disrupted by upregulation of ammonia-generating enzymes, such as glutaminase (GLS), which generates ammonia from glutamine, and causes concurrent downregulation of ammonia-detoxifying pathways, including OTC and glutamine synthetase (GS) [18]. This creates a net positive generation of ammonia by the tumor itself, which overwhelms the hepatic function of the residual non-cirrhotic liver in FLHCC patients, causing paraneoplastic HAE. This metabolic rewiring of the tumor, characterized by glutamine dependence and creation of a nutrient-depleted tumor immune microenvironment rich in immunosuppressive metabolites (eg, ammonia, acidosis), prevents an effective antitumor immune response.

In conventional HCC, the key urea cycle enzyme carbamoyl phosphate synthetase 1 (CPS1), which detoxifies ammonia in the liver, is depleted through hypermethylation of its promoter, resulting in accumulation of ammonia [19]. c-Myc overexpression is seen in up to 70% of viral and alcohol-related conventional HCC [20]. CPS1 deficiency also stabilizes the c-Myc protein by inhibiting the ubiquitin-proteasome system and preventing its degradation [19]. This c-Myc upregulates glutamine synthetase (GS), unlike in FLHCC, which consumes ammonia by converting glutamate into glutamine, which participates in nucleotide synthesis and amino acid transport, essential for the proliferation and growth of the tumor cells [21]. Thus, in conventional HCC, there is no net accumulation of toxic ammonia to cause paraneoplastic HAE. Furthermore, conventional HCC most frequently arises in cirrhotic livers. Hyperammonemia and the consequential HAE in these patients result from hepatic insufficiency and portosystemic shunting rather than as a paraneoplastic phenomenon, which is more amenable to conventional treatment of HAE.

Although DNAJB1-PRKACA fusion is seen in 80% of FLHCC patients, HAE is seen only in a rare handful of cases. Prior studies have shown that subclinical hyperammonemia in FLHCC is more common than clinically recognized, affecting approximately one-third (31.3%) of patients [22]. However, the manifestation of overt HAE requires additional clinical factors such as high tumor burden, extensive hepatic dysfunction (reducing functional metabolic reserve), and host-specific factors such as nutritional status, sarcopenia, renal clearance, and concurrent triggers (e.g., infection, dehydration, chemotherapy-induced tumor lysis, or catabolic stress). Together, these factors overwhelm systemic ammonia clearance. In our patient, the bulky metastatic disease, loss of hepatic metabolic reserve due to metastasis to the liver, prior partial hepatectomy, cachexia with loss of muscle mass, and catabolic stress all may have contributed to the development and refractory nature of HAE.

One limitation of our study is that we postulate the mechanism of hyperammonemia based on prior literature and biological plausibility. Molecular testing for the OTC gene, the OTC and ODC enzymatic activities, or the activation of c-Myc in tumor tissue was beyond the scope of our study. This merits further research in future cases of FLHCC. Though our patient had a large liver lesion measuring 7.6 × 7.9 cm in segment 7 of the liver and a partial hepatectomy with resection of the left lobe of the liver, there was no cirrhosis, splenomegaly, or other imaging evidence of portal hypertension or portosystemic shunting on CT to suggest an alternate mechanism of hyperammonemia. Hence, based on biochemical evidence, we conclude the most probable cause of HAE was an acquired urea cycle defect with OTC deficiency.

Timely diagnosis and prompt treatment of HAE are required to prevent serious complications and permanent neurological sequelae. Due to the rarity of such presentations in cancer patients, especially FLHCC, there is no consensus on treatment. However, it is extrapolated from anecdotal reports of HAE in other disorders. Baseline ammonia level should be checked in all patients with FLHCC irrespective of liver function. If serum ammonia level is high, it is prudent to check for urea cycle defect with quantitative plasma amino acids, and urinary organic acids, including orotic acid. Low citrulline level in the blood and elevated urine orotic acid are the hallmark of OTC deficiency. Molecular testing for the OTC gene helps diagnose inherited defects of the urea cycle, and an enzymatic assay of OTC can be performed on liver tissues. Referral to a metabolic specialist is often recommended.

Treatment is directed at reducing ammonia production, removing excess ammonia from the body, and treating any inciting factors. The nitrogen load is reduced by eliminating protein from the diet while ensuring sufficient fluids with dextrose and electrolytes. This helps to prevent excess catabolism and dehydration, which itself may predispose patients to HAE [1]. Drugs such as rifaximin, a non-absorbable antibiotic, decrease colonic deaminating bacteria and thus reduce ammonia production in the gut. While rifaximin is effective in HAE associated with advanced liver failure, there is little evidence and unclear benefit for use in cancer-associated HAE. Lactulose, a non-absorbable disaccharide, acidifies the colon and converts

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ammonia into ammonium ion, thus preventing its absorption and eliminating ammonia from the body. However, the gastrointestinal adverse effects of lactulose can interfere with quality of life. Ammonia scavenger therapy with intravenous sodium benzoate and sodium phenylacetate at a dose of 5.5 g/m^2, along with intravenous arginine 2 to 6 g/m^2, is effective for the treatment of acute episodes of cancer-associated HAE. Scavenger therapy is recommended for a serum ammonia level of more than 100 µmol/L [1]. Sodium benzoate converts glycine to hippurate, and sodium phenylacetate converts glutamine to phenylacetate glutamine (PAG), which are non-urea forms of ammonia and are removed from the body by the kidneys [23]. Arginine helps in mitigating HAE by providing a substrate for the urea cycle. However, the serum ammonia level in our patient remained refractory to treatment with 2 sessions of scavenger therapy. In such refractory cases, for acute treatment of HAE, intermittent hemodialysis or continuous arteriovenous or venovenous hemofiltration is a quick and efficient way to reduce serum ammonia levels. Hemodialysis is recommended until the serum ammonia level falls below 200 µmol/L for at least 24 hours [24]. In our patient, the serum ammonia level remained refractory to even hemodialysis, and his neurological status continued to worsen. We postulate the high tumor burden from his metastatic disease, as seen on imaging, and the paraneoplastic acquired urea cycle defect led to the precipitation of refractory hyperammonemia and consequential clinical deterioration.

Mitigating refractory HAE in FLHCC may require targeting the underlying paraneoplastic mechanism. In a phase II study of ENMD-2076, a selective aurora kinase A inhibitor, 1 out of 35 enrolled patients showed a partial response, and 20 patients had stable disease, with a reported median overall survival of 19 months [25]. Encephalopathy was reported in 2 patients as an adverse event. The study failed to show any clinical benefit of ENMD-2076 as a single agent in FLHCC. Other potential therapeutic targets include glutamine antagonism with DRP-104 (sirpiglenastat). DRP-104 is a novel prodrug that gets converted to the active form 6-diazo-5-oxo-L-norleucine (DON) in tumor cells and exhibits glutamine antagonism [26]. A phase 1b/2 clinical trial (NCT06027086) is currently ongoing to evaluate DRP-104 plus the immune checkpoint inhibitor (ICI) durvalumab in advanced FLHCC, aiming to overcome immune resistance by reprogramming the tumor immune microenvironment and improving response to prior ICI therapy [27]. CB-839 (telaglenastat), a glutaminase 1 inhibitor, combined with nivolumab, is currently being tested in patients with advanced solid tumors (metastatic melanoma, renal cell carcinoma, and non-small-cell lung cancer) in a phase I/II trial [28]. A previous study with the mTOR (mechanistic target of rapamycin) inhibitor, Everolimus, failed to demonstrate clinical benefit in advanced FLHCC [29]. An ODC inhibitor, alpha-difluoromethylornithine (DFMO), which depletes polyamine pools and induces cell cycle arrest in neuroblastoma cells, could potentially play a therapeutic role in FLHCC cases [30]. Further clinical trials are required to explore these potential therapeutic avenues.

Conclusions

HAE is a rare paraneoplastic presentation of FLHCC. Early diagnosis and treatment are important to improve outcomes and prevent permanent neurological sequelae. Unlike encephalopathy related to advanced liver failure, lactulose and rifaximin have limited clinical benefit. However, ammonia-scavenging agents, such as sodium benzoate and sodium phenylacetate, along with arginine supplementation, are effective in mitigating episodes of acute encephalopathy by excreting ammonia from the body. Intermittent hemodialysis or continuous arteriovenous or venovenous hemofiltration also quickly reduces serum ammonia levels and can be used as a last resort in refractory cases. However, patients with refractory HAE who fail to improve even with dialysis have few other options available and often require a multidisciplinary approach, including palliative care. Further studies are required to investigate the clinical benefit of novel agents targeting the paraneoplastic pathway.

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Patient Permission/Consent Declarations

Consent obtained.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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