Case Report

# A case of hyperammonemia occurring during treatment of metastatic renal cell carcinoma with axitinib

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**Abbreviations & Acronyms**
AE = adverse event
ALT = alanine aminotransferase
AST = aspartate aminotransferase
BID = bis in die
GIST = gastrointestinal stromal tumor
HCC = hepatocellular carcinoma
mRCC = metastatic renal cell carcinoma
N.D. = no data
PNET = primitive neuroectodermal tumor
RCC = renal cell carcinoma
TKI = tyrosine kinase inhibitor
TSH = thyroid stimulating hormone
VEGFR = vascular endothelial growth factor receptor

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**Introduction:** Although the incidence of hyperammonemia as an adverse event of tyrosine kinase inhibitors is quite low, several cases of tyrosine kinase inhibitor associated hyperammonemia have been reported. We report a case of hyperammonemia, that occurred during combined treatment with axitinib and pembrolizumab in a metastatic renal cell carcinoma patient without hepatic disorder or liver metastases.

**Case presentation:** A 77-year-old Japanese woman was diagnosed with metastatic renal cell carcinoma and was treated with pembrolizumab and axitinib. Both agents were subsequently discontinued due to hyperammonemia with hypothyroidism. After recovery, the patient resumed single-agent therapy with axitinib. However, hyperammonemia and hypothyroidism occurred again, suggesting axitinib-inducible adverse event. After nephrectomy, a lower dose of axitinib was restarted and continued safely for residual metastases under prophylactic treatment with aminoleban, lactulose, and levothyroxine.

**Conclusion:** The rare occurrence of hyperammonemia should be considered during treatment with VEGFR- targeted tyrosine kinase inhibitor including axitinib, and supportive prophylactic medication may be useful.

**Key words:** axitinib, hyperammonemia, hypothyroidism, renal cell carcinoma, tyrosine kinase inhibitor.

## Keynote message

Hyperammonemia during axitinib treatment is rare but should be carefully monitored.

## Introduction

A recent standard treatment for mRCC is the combination therapy of an immune checkpoint inhibitor and a TKI. Combined treatment with pembrolizumab and axitinib have shown significant efficacy compared to sunitinib in phase III clinical trials.[1] As treatment related Grade 3 or worse AEs, hypertension (22%), alanine aminotransferase increase (13%), diarrhea (9%), and hypothyroidism (0.2%) have been reported; to date, however, hyperammonemia has not been observed. In addition, no cases with single use of axitinib have been reported. We report a case of hyperammonemia that occurred during combined treatment of axitinib and pembrolizumab in a mRCC patient without hepatic disorder or liver metastases.

## Case presentation

A 77-year-old Japanese woman visited her family doctor with a chief complaint of impaired consciousness. Blood tests revealed anemia, and computerized tomography scan indicated a left hypervascular renal tumor suggesting RCC with multiple lung metastases (Fig. 1). At this time, the cause of the impaired consciousness was inferred to be anemia, and blood ammonia

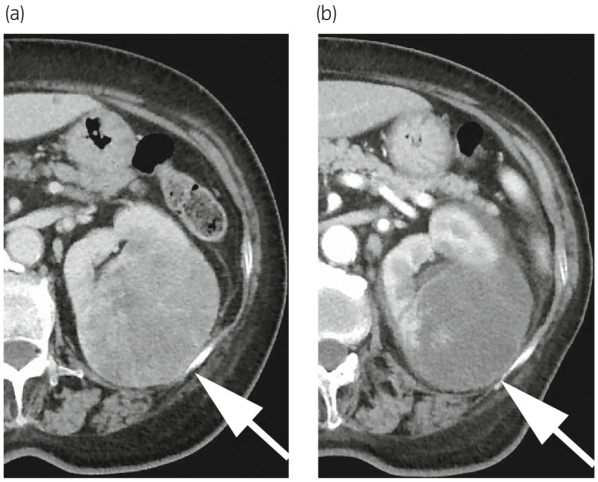


**Fig. 1** Computed tomography scans of the abdomen: diffusely enhanced tumor (87 mm diameter in size) was observed in left kidney (white allow, a). After pharmacotherapy, the tumor shrunk to 72 mm, and the internal density became low (white allow, b). Containing of necrosis was suggested.

levels were not measured. She was referred to the urology department. She reported a past history of appendicitis, cerebral stroke, and comorbidities of hypertension and hyperlipidemia. She reported no allergies and no family history of cancer. Combination treatment of pembrolizumab 200 mg/body/3 weeks and axitinib 5 mg BID was started for mRCC (cT3aN0M1). After 43 days, the patient visited our hospital due to impaired consciousness, and blood tests showed hyperammonemia (127 μmol/L), Grade1 liver dysfunction (AST/ALT: 57 IU/L/36 IU/L), grade 3 hypoalbuminemia (19 g/L) and Grade2 hypothyroidism (TSH: 29.09 mU, FT3/FT4: 19.43 pmol/L/1.18 pmol/L). Since the patient had no coexisting liver disease and did not have any risk factors for hyperammonemia, such as constipation, urinary tract infection, dehydration, excessive protein intake, or sedatives/antiepileptic drugs, we suspected autoimmune hepatitis and associated hyperammonemia caused by pembrolizumab. After withdrawal of both pembrolizumab and axitinib, treatment with lactulose and aminoleban for hyperammonemia and levothyroxine (25 μg) for hypothyroidism was initiated. Serum ammonia levels improved promptly to the normal range on the second day of hospitalization, and the patient was discharged on the seventh day. Therefore, single use of low dose (2 mg BID) axitinib was resumed. Since thyroid function also improved, the patient was also discontinued on levothyroxine. However, 36 days after resumption, the patient presented to the emergency room again with impaired consciousness and was readmitted with hyperammonemia (109 μmol/L) and hypothyroidism. We consulted a hepatologist to clarify the cause of the hyperammonemia; however, there was no evidence of liver failure, portal vein shunts, urease-producing bacterial infections, or gastrointestinal bleeding, which are the most common causes of hyperammonemia. Similar to the previous hospitalization, serum ammonia levels improved promptly to the normal range following withdrawal of axitinib. We suspected drug-induced hyperammonemia due to axitinib. After recovery, left nephrectomy was planned because favorable treatment outcome was observed in primary site (SD) and lung metastasis (PR). To avoid the risk of tumor progression due to withdrawal of axitinib, we resumed treatment with axitinib at a very low dose of 1 mg BID with oral intake of lactulose and aminoleban to prevent hyperammonemia and levothyroxine (25 μg) for hypothyroidism. Subsequent hyperammonemia was not observed, and the patient underwent laparoscopic left nephrectomy with lymph node dissection. Pathological diagnosis revealed clear cell carcinoma (Fig. 2). Thereafter, she resumed treatment with axitinib 2 mg BID for residual lung

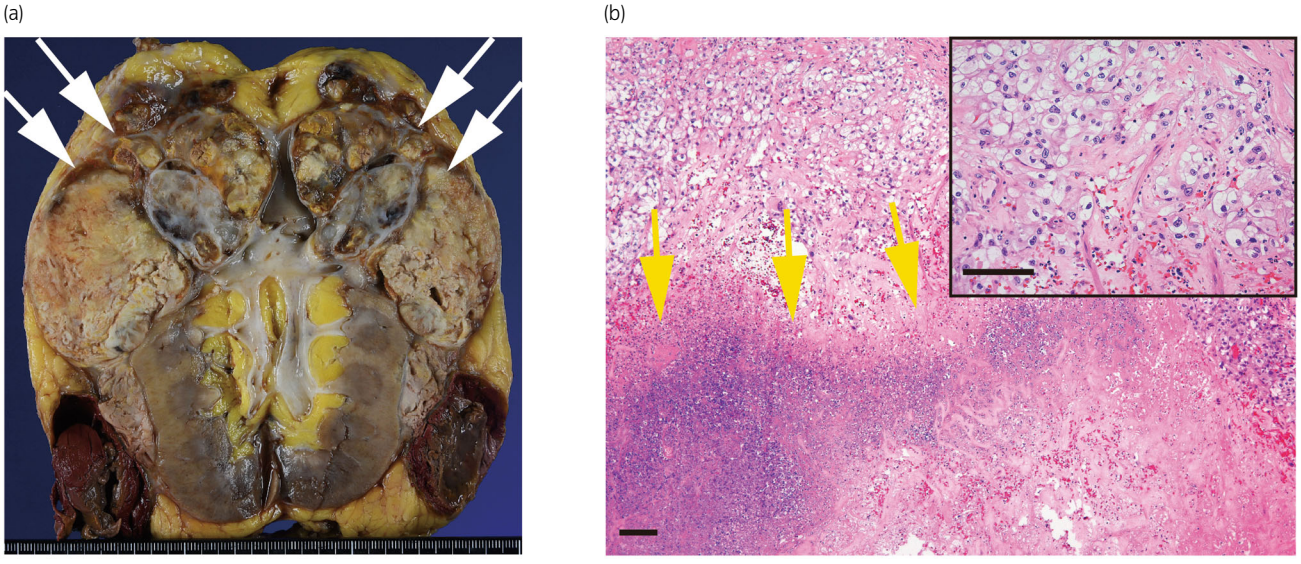


**Fig. 2** Macro and microscopic appearance is shown: yellowish-white tumor with necrosis located in the upper pole of the left kidney (white allows, a). Large amount of necrosis was observed (yellow allows, b), and cancer cells with clear cytoplasm proliferated in alveolar pattern (upper side, scale bars: 100 μm, b). Pathological diagnosis was compatible for clear cell RCC.

metastases with oral intake of lactulose and aminoleban to prevent hyperammonemia (Fig. 3). Although an increased dose of levothyroxine (50 μg) was necessary for hypothyroidism, the patient remained symptom free for 168 days without either hyperammonemia or expansion of lung metastases.

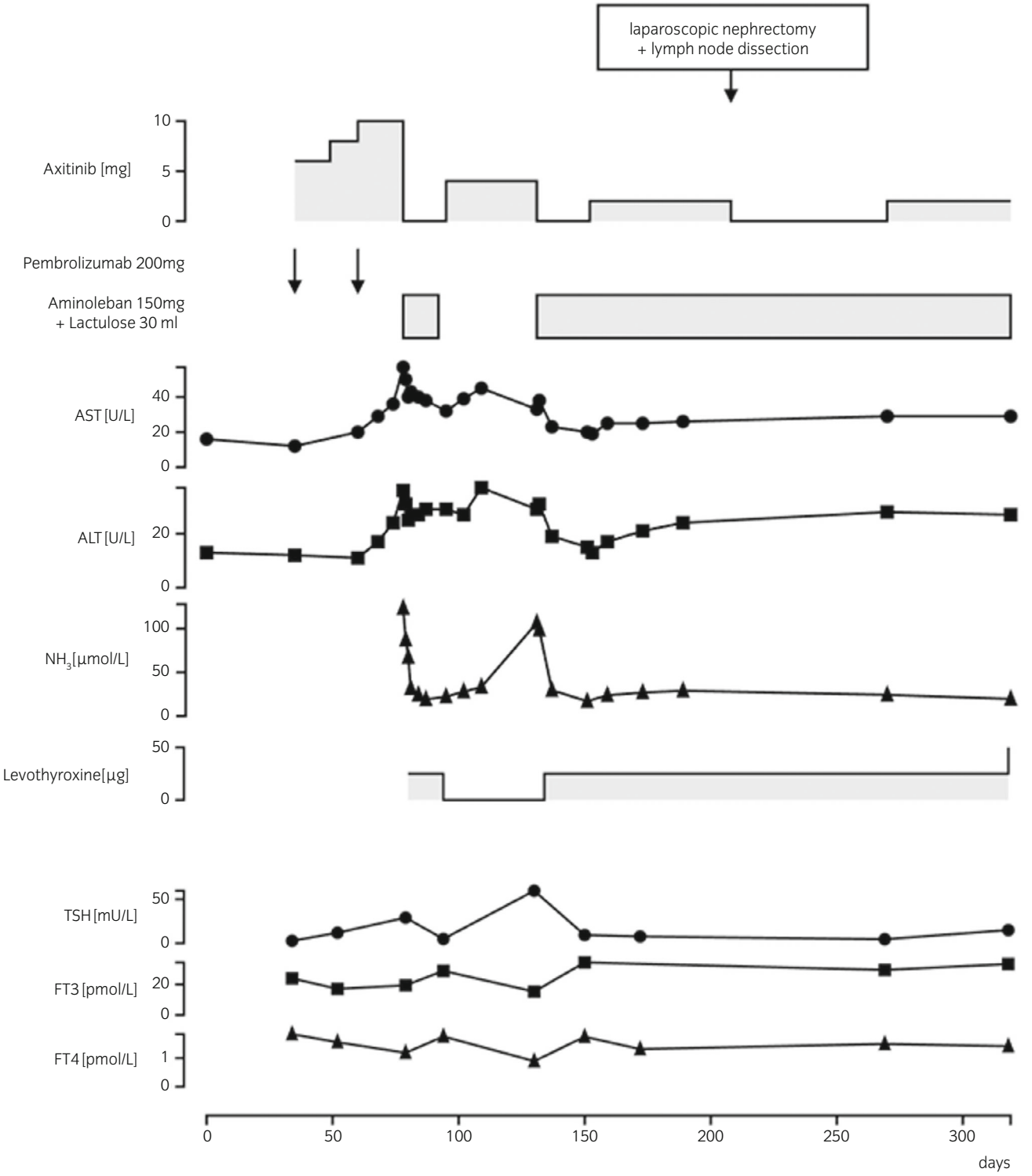


**Fig. 3** Clinical course: Dosage is shown in areas. Downward arrows indicate pembrolizumab medication or surgery. In the upper part, ● indicates AST (U/L), ■ indicates ALT (U/L), and ▲ indicates $NH_3$ (μmol/L). In the lower part, ● indicates TSH (mU/L), ■ indicates Free T3 (FT3) (pmol/L), and ▲ indicates Free T4 (FT4) (pmol/L).

## Discussion

In clinical trials with single use of axitinib (AXIS study),[2] AST and ALT elevations were 6.7% and 8.1% for all grades, respectively, as AEs; however, no patients with elevated transaminases were reported in the Japanese cohort, whereas, the combined therapy of pembrolizumab and axitinib (KEYNOTE-426 study)[1] revealed patients with increased AST in 22.6% and increased ALT in 23.8% (all grades), including 2.8% of autoimmune hepatitis. Although, no patients with hyperammonemia were reported in the above studies, we considered the possibility that the hyperammonemia might be caused by prolonged immune-related AEs due to pembrolizumab because a higher incidence of transaminase was observed in combined therapy. However, restart of axitinib after withdrawal of pembrolizumab induced recurrence of hyperammonemia, and improved with the cessation. Therefore, we concluded that hyperammonemia was caused by axitinib. We found several previous reports of hyperammonemia caused by sunitinib, a similar VEGFR-targeted TKI.[3–9] In addition, hyperammonemia was also reported in a case of sorafenib[9] and regorafenib.[8] In these reports, cases with liver metastases, hepatocellular carcinoma or liver cirrhosis were included. Similar to our case, however, cases without apparent liver disease were also reported. To the best of our knowledge, the current case is the first report describing hyperammonemia associated with axitinib (Table 1). As the mechanisms of sunitinib-induced hyperammonemia, decreased ability of the liver for handling $NH_3$ due to antiangiogenic effect, increased N-desethyl metabolite which is the primary metabolized product of sunitinib by CYP3A4 and ethnic difference with genetic polymorphism in pharmacokinetics were discussed; however, the mechanism is not well understood.[9,10] In light of similar case reports of hepatic encephalopathy induced by Sorafenib,[9] Regorafenib,[8] and Sunitinib,[4] it was reasonably suspected to be a result of a class effect of these TKIs. In this case, as an additional mechanism of or associated factor in hyperammonemia, the simultaneously complicated hypothyroidism, as a side effect of axitinib was suspected, retrospectively. Hypothyroidism aggravates the hyperammonemic state due to an increased nitrogen load that decreases protein synthesis, increases protein catabolism and decreases intestinal motility, which promotes the bacterial production of ammonia and augments its absorption.[11,12] Additionally, hypothyroidism may enhance the toxicity of ammonia in the brain, and a case of sunitinib induced hyperammonemia and simultaneous hypothyroidism was reported previously.[13] To clarify the relevance of those side effects further investigation is needed. In this case, levothyroxine was promptly supplemented with lactulose and aminoleban, and the level of thyroid hormone returned to and was maintained at normal levels. Since the patient did not wish to receive additional surgical intervention for lung metastases, we continued low-dose axitinib (2 mg BID) with oral intake of lactulose and aminoleban to prevent hyperammonemia (Supplemental comment 1). Risk factors for hyperammonemia include constipation, urinary tract infections, dehydration, excessive protein intake, and sedative/

**Table 1** Summary of characteristics of previously reported cases with TKI-associated hyperammonemia

| Case | Tumor | Liver condition | Days between drug initiation and encephalopathy | Ammonia level (μmol/L) | Suspected drug | Treatment | Days to recovery |
|---|---|---|---|---|---|---|---|
| Our patient—1st admission | RCC | ALT 36 U/L, AST 57 U/L | 43 | 127 | Axitinib | Aminoleban 150 g/day + lactulose 3×/day | 2 |
| Our patient—2nd admission | | ALT 29 U/L, AST 33 U/L | 36 | 109 | Axitinib | Aminoleban 150 g/day + lactulose 3×/day | 2 |
| Haloon et al.[3] | RCC | Cirrhosis ALT 20 U/L, AST 27 U/L | 44 | 122 | Sunitinib | Dialysis + lactulose 3×/day | 4 |
| Lee et al.[4] | GIST (small bowel) | Liver metastasis ALT 50 U/L, AST 79 U/L | 14 | 150 | Sunitinib | Lactulose hourly | 1 |
| Lee et al.[4] | GIST (caecum) | ALT 53 U/L, AST 44 U/L | 10 | 277 | Sunitinib | Lactulose (ensure bowel opening 3×/day) | 1 |
| Shea et al.[5] | PNET | Liver metastasis ALT 43 U/L, AST 53 U/L | 14 | 147 | Sunitinib | Lactulose hourly | 1 |
| Pilanci et al.[6] | RCC | ALT 25 U/L, AST 34 U/L | 14 | 104 | Sunitinib | Lactulose (frequency not mentioned) | 7 |
| Lipe et al.[7] | Infiltrating ductal carcinoma of breast with metastasis to liver | Liver metastasis ALT 54 U/L, AST 100 U/L | 12 | 202 | Sunitinib | None | 12 |
| Kuo et al.[8] | GIST | ALT 36 U/L | 395 | 105 | Regorafenib | Lactulose | 2 |
| Brandi et al.[9] | HCC | N.D. | N.D. | 657 | Sorafenib | None | 14 |

antiepileptic drug administration. Patients with these risk factors, including those with liver metastases or chronic hepatitis, should be cautioned against developing hyperammonemia. The prophylactic medication seemed to be effective without additional AEs, suggesting one measure for such cases (Supplemental comment 2).

## Conclusion

We reported a case of axitinib-inducible hyperammonemia. VEGFR- targeted TKI was usually used for mRCC. Although the exact mechanism of TKI-induced hyperammonemia is unknown, the rare occurrence of hyperammonemia should be considered and prophylactic medication for hyperammonemia should be considered, if necessary. Furthermore, if hypothyroidism occurs, more attention should be paid to the development of hyperammonemia. In addition, supplementation with thyroid hormone is also important.

## Author contributions

Shoichi Kimura: Investigation; writing – original draft. Yukiya Fujisaki: Investigation. Chie Onizuka: Investigation. Satoru Hasuike: Formal analysis; writing – review and editing. Yuichiro Sato: Formal analysis. Shoichiro Mukai: Supervision; writing – review and editing. Toshiyuki Kamoto: Supervision.

## Conflict of interest

The authors declare no conflict of interest.

## Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

## Informed consent

Not applicable.

## Registry and the Registration No. of the study/trial

Not applicable.

## References


1 Powles T, Plimack ER, Soulieres D *et al*. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2020; **21**: 1563–73.

2 Rini BI, Escudier B, Tomczak P *et al*. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomized phase 3 trial. *Lancet* 2011; **378**: 1931–9.

3 Haroon S, Ko S, Wong A, Tan PS, Lee E, Lau T. Sunitinib-associated hyperammonemic encephalopathy successfully managed with higher intensity conventional hemodialysis: a case report. *Medicine* 2021; **100**: e24313.

4 Lee NR, Yhim HY, Yim CY *et al*. Sunitinib-induced hyperammonemic encephalopathy in gastrointestinal stromal tumors. *Ann. Pharmacother.* 2011; **45**: e56.

5 Shea YF, Chiu WY, Mok MY *et al*. Sunitinib-induced hyperammonaemia in a patient with pancreatic neuroendocrine tumour. *J. Clin. Pharm. Ther.* 2013; **38**: 327–9.

6 Pilanc KN, Elbüken F, Ordu C *et al*. A rare case of sunitinib-induced hyperammonemic encephalopathy and hypothyroidism in metastatic renal cell carcinoma. *Am. J. Ther.* 2016; **23**: e583–7.

7 Lipe DN, Hoxha B, Sahai SK. Sunitinib-associated hyperammonemic encephalopathy. *Am. J. Emerg. Med.* 2021; **46**: 282–3.

8 Kuo JC, Parakh S, Yip D. Regorafenib-induced hyperammonemic encephalopathy. *J. Clin. Pharm. Ther.* 2014; **39**: 446–8.

9 Brandi G, de Rosa F, Calzà L *et al*. Can the tyrosine kinase inhibitors trigger metabolic encephalopathy in cirrhotic patients? *Liver Int.* 2013; **33**: 488–93.

10 Deeks ED, Keating GM. Sunitinib. *Drugs* 2006; **66**: 2255–6.

11 Marti J, Portoles M, Jimenez-Nacher I *et al*. Effect of thyroid hormones on urea biosynthesis and related process in rat liver. *Endocrinology* 1988; **123**: 2167–74.

12 Rimar D, Kruzel-Davila E, Dori G, Baron E, Bitterman H. Hyperammonemic coma—barking up the wrong tree. *J. Gen. Intern. Med.* 2007; **22**: 549–52.

13 Díaz-Fontenla F, Castillo-Pradillo M, Díaz-Gómez A *et al*. Refractory hepatic encephalopathy in a patient with hypothyroidism: another element in ammonia metabolism. *World J. Gastroenterol.* 2017; **23**: 5246–52.


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