Chung Shan Medical Journal 2021; 32:101-104

Case Report

Idiopathic hyperammonemic encephalopathy after chemotherapy in a patient with rectal cancer

Jui-Hung Chen[1], Pei Lin[1], Hsin-Hsin Huang[2] ,Chien-Han Tsao[3,4*]

[1] Department of Critical Care, Nantou Christian Hospital, Nantou, Taiwan
[2] Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan
[1] Department of Otolaryngology, Chung Shan Medical University Hospital, Taichung, Taiwan
[1] School of Medicine, Chung Shan Medical University, Taichung, Taiwan

Idiopathic hyperammonemic encephalopathy is a rare complication of chemotherapy that has been described in patients with hematological malignancy, colon cancer, and hepatocellular carcinoma in the presence of noncirrhotic liver. The cause of this syndrome, which can be fatal, is not well understood. We present a case of rectal cancer without underlying liver dysfunction who suffered abrupt alteration in mental status after the first course of chemotherapy. Ammonia-lowering therapy was started immediately, without cessation of chemotherapy. For additional courses of chemotherapy, reduction to 75% of normal dosage was found to be safe and to produce satisfactory results.

Keywords: Idiopathic hyperammonemic encephalopathy, Hepatic insufficiency, 5-Fluorouracil

Introduction

Ammonia is a waste product that originates from proteins metabolized by bacteria in the intestine. The liver detoxifies ammonia in the urea cycle to produce urea that is excreted by the kidneys. If the liver is unable to convert ammonia to urea, hyperammonemia may develop, leading to progressively worsening mental status, confusion, sleepiness, hand tremors, respiratory alkalosis, and coma[1]. Idiopathic hyperammonemic encephalopathy is a rare complication of chemotherapy that has been described in patients with hematological malignancy, colon cancer, and hepatocellular carcinoma in the presence of noncirrhotic liver[1-5]. It can lead to death if allowed to progress[1,9,10]. The cause of this syndrome is not well known. However, it might be associated with the malignancy itself or with chemotherapy[5-8]. Treatment methods for idiopathic hyperammonemic encephalopathy include drugs, such as carglumic acid (a synthetic analog of the product of N-acetylglutamate synthase)[2] , arginine (an essential amino acid)[2], metronidazole, and carnitine (a water-soluble vitamin)[3], hemodialysis, and cessation of chemotherapy[4] .

* Correspondence Author: Chien-Han Tsao
Address: No. 110, Sec. 1, Jianguo N. Rd., South District, Taichung City 40201, Taiwan.
Tel: +886-4-24730022 ext. 34812
E-mail: Q1203738@gmail.com

Case report

A 71-year-old male patient presented with adenocarcinoma of rectum (pT3N1Mo, stage IIIb) and underwent radical resection for rectal cancer and colorectal anastomosis about one month before admission for first course of chemotherapy. His medical history included type 2 diabetes mellitus, mixed hyperlipidemia, right renal cyst, and mild fatty change in liver with mild splenomegaly based on systemic examinations. Serum levels of aspartate transaminase and alanine transaminase were in the normal range and there was no sign of

hepatitis or other severe liver dysfunction before or after chemotherapy or the occurrence of idiopathic hyperammonemic encephalopathy. This patient was in stable condition before the first course of chemotherapy which consisted of 5126mg total dose 5-Fluorouracil (loading: 400mg/sqM, 732mg; first day: 1200mg/sqM, 2197mg; second day: 1200mg/sqM, 2197mg). Near the completion of the first course of full-dose chemotherapy, mental status change (from GCS:E4M6V5 to GCS:E4M4V3) was noted. Arterial gas analysis showed respiratory alkalosis (PH:7.451, PaCO2:23.4mm Hg, Pa O2:95.8mmHg, HCO3-:16.4mEq/L) with elevation of serum ammonia level to 696ug/dL. This patient was treated immediately with lactulose 200cc and Neomycin 2000mg enema, without cessation of chemotherapy. No specific finding was noted on brain computed tomography. The patient recovered consciousness about 10 hours later. Serum ammonia level returned to normal (39ug/dL) 15 hours later. The patient was well and discharged from the hospital after 4 days with no neurological signs.

Dosage of 5-Fluorouracil for the second and third courses of chemotherapy was half that of the first course. Although mild hyperammonemia (145ug/dL and121ug/dL, respectively) was noted, this patient did not suffer mental status change or respiratory alkalosis. After oral administration of lactulose, serum ammonia level reverted to normal (44ug/dL,11ug/dL, respectively) before the patient was discharged from the hospital. Subsequently,75% of normal dosage of 5-Fluorouracil was administered during the fourth course of chemotherapy and the result was similar to that of the second and third courses. Therefore, 75% of normal dosage of 5-Fluorouracil was employed for the following courses. The results of therapy were satisfactory.

Discussion

Liver disease-induced hyperammonemia often causes change in mental status. Idiopathic hyperammonemic encephalopathy is defined as plasma ammonia level greater than twice the upper limit of normal, with relatively normal liver function and absence of identifiable cause[4]. This syndrome was first reported in the 1980s as a complication of acute leukemia treatment. Since then, it has been described in patients with colon cancer and hepatocellular carcinoma without cirrhotic liver[1-7]. It might be associated with the malignancy itself or with chemotherapy. To date, the pathophysiology remains unclear. Based on previous studies, one probable cause is that the liver is unable to detoxify ammonia in the urea cycle to produce urea. Or, deficiency in an undetermined metabolite leads to inhibition of N-acetylglutamate synthase, a urea cycle enzyme. Reports of idiopathic hyperammonemic encephalopathy treated with L-arginine have suggested a functional arginine deficiency secondary to chemotherapy-induced catabolism. Arginine has multiple metabolic fates. It not only serves as a precursor for synthesis of proteins, nitric oxide, creatine, polyamines, and agmatine, but also as an activator of N-acetyl glutamate synthase[2].

Although some mortalities have been reported[1, 9, 10], patients with idiopathic hyperammonemic encephalopathy can fully recover[3] with rapid diagnosis and treatment. Carglumic acid and arginine have been demonstrated to be successful treatments for idiopathic hyperammonemic encephalopathy. Cessation of parenteral alimentation to lower protein intake, administration of lactulose, omeprazole, metronidazole, or carnitine, and hemodialysis have also been described. Some authors have suggested cessation of chemotherapy. There is no single conclusion or dosage standard for idiopathic hyperammonemic encephalopathy[1-10]. This patient was treated with immediate lactulose enema only and mental status recovered quickly without cessation of chemotherapy. The doses of chemotherapy were halved over the following two courses and increased to 75% of normal for the subsequent courses.

Based on laboratory results, there were two hyperammonemia events during the following courses of chemotherapy. However, the situation was not critical and the serum ammonia level returned to normal quickly without recurrent mental status change.

Compared to previous reports, this case showed that cessation of chemotherapy is not necessary. Reduction to 75% chemotherapy dose for patients with idiopathic hyperammonemic encephalopathy

is feasible. Early recognition and prompt medical intervention are important.

The limitation of this report is that a single case cannot be used to confirm diagnosis and management. Due to the unclear pathophysiology of idiopathic hyperammonemic encephalopathy and the role of chemotherapy, further studies are needed to verify the chemotherapy dosage in the event of idiopathic hyperammonemic encephalopathy and the impact on long-term survival of cancer.

Conclusion

Idiopathic hyperammonemic encephalopathy should be considered when there is mental status change after chemotherapy. Early recognition is important. Satisfactory results can be obtained with relatively inexpensive and conventional medical treatments without cessation of chemotherapy, if ammonia-lowering therapy is started quickly. Patients may be able to tolerate continuing chemotherapy at 75% of the normal dosage.

References

1. Gedik H, Yokus O (2015) Hyperammonemia Associated Encephalopathy in Two Cases with Hematological Malignancy. Int J Cancer Res Mol Mech 1(4)
2. Lazier J Lupichuk SM Sosova I et al. Hyperammonem ic encephalopathy inan adenocarcinoma patient managed with carglumic acid. Curr Oncol. 2014; 21(5): e736–e739
3. Frere P, Canivet JL Gennigens C, et al. Hyperammonemia after high dose chemotherapy and stem cell transplantation. Bone Marrow Transplant. 2000;26(3):343-5.
4. Chen YH, Chiou TJ, Hsu YN, Liu CY. Idiopathic hyperammonemia after chemotherapy with vinorelbine, topotecan, and cisplatin in a patient with acute lymphocytic leukemia. Hematol Oncol Stem Cell Ther . 2010;3(4):199-202.
5. Chang YY, Lin JK, Jiang JK. OxaliplatinChang YY, Lin JK, Jiang JK. Oxaliplatin-related hyperammonaemic encephalopathy in a patient with colon cancer. Colorectal Dis . 2012;14(12):e821.
6. Winter SS, Rose E, Katz R.. Hyperammonemia after chemotherapy in an Winter SS, Rose E, Katz R. Hyperammonemia after chemotherapy in an adolescent with hepatocellular carcinoma. J Pediatr Gastroenterol Nutr 1997;25(5):537-40.
7. Espinós J, Rifón J, Pérez-Calvo J, Nieto Y. Idiopathic hyperammonemia Calvo J, Nieto Y. Idiopathic hyperammonemia following high-dose chemotherapy. Bone Marrow Transplant 2006;37(9):899.
8. Willson KJ, Nott LM, Broadbridge VT, Price T. Hepatic encephalopathy associated with cancer or anticancer therapy. Gastrointest Cancer Res. 2013;6(1):11-6.
9. Jaing TH, Lin JL, Lin YP, Yang SH, Lin JJ, Hsia SH. Hyperammonemic encephalopathy after induction chemotherapy for acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2009;31(12):955-6
10. Mitchell RB, Wagner JE, Karp JE, Watson AJ, Brusilow SW, Przepiorka D, Storb R, Santos GW, Burke PJ, Saral R. Syndrome of idiopathic et al. Syndrome of idiopathic hyperammonemia after high-dose chemotherapy: review of nine case. Am J Med; 1988;85(5):662-7.