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A case report of hyperammonemic encephalopathy induced by high-dose continuous infusion of 5-fluorouracil in a patient with rectal cancer

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Abstract

Background: Hyperammonemia caused by high-dose infusion of 5-fluorouracil (5-Fu) is a rare adverse reaction in patients with rectal cancer. There are very few reports of hyperammonemia caused by 5-Fu in domestic and foreign literatures, however, deficiency of DihydroPyrimidine Dehydrogenase (DPD) and the influence of 5-Fu metabolites may be the pathogenic mechanisms of encephalopathy. Muscle loss, renal insufficiency and infection also has played an important role in the occurrence.

Case description: A 67-year-old Chinese man was diagnosed with a rectal cancer. The patient had been using Xylodase for 17 months, which was a long treatment cycle, followed by a high-dose intravenous treatment with 5-Fu, which led to the development of hyperammonemic encephalopathy. The patient developed hyperammonemic encephalopathy after the forth and the fifth cycle of chemotherapy (FOLFIRI) with a significant increase in blood ammonia level and corresponding symptoms of encephalopathy, such as unclear consciousness, unresponsive to stimuli, and stiff limbs, etc. Fortunately, all of those laboratory indicators and vital signs turned to be normal after interrupting use of 5-Fu and corresponding treatments during the last two cycles.

Conclusion: A decrease in the number of DPD and the muscle loss in the patient which led to damage to the tricarboxylic acid cycle can explain the increase of the ammonia in blood. It is recommended to conduct a comprehensive evaluation of the patient's physical condition before chemotherapy to avoid the use of 5-Fu in cases of infection or dehydration. TDM can be considered to monitor blood drug concentration and guide the 5-Fu dosage if possible.

Keywords: Case report; Hyperammonemic encephalopathy; High-dose continuous infusion of 5-Fu.

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Introduction

5-fluorouracil, also known as 5-Fu, is a commonly used chemotherapy drug for solid tumors, which is used to treat gastrointestinal malignancies, ovarian cancer, lung cancer, etc. Its common adverse reactions include bone marrow suppression, gastrointestinal reactions, and occasionally oral mucositis, cerebellar ataxia, while long-term use can cause neurotoxicity. However, there are very few reports of hyperammonemia caused by 5-fluorouracil in domestic and foreign literatures. In the present case, the patient developed hyperammonemic encephalopathy due to continuous infusion of high-dose 5-fluorouracil, which was analyzed to be highly correlated with the toxic side effects of 5-fluorouracil. This is an extremely rare occurrence and is described below. We present the following case in accordance with the CARE reporting checklist.

Case presentation

The patient (67-year-old, male, case number 20200*****) was diagnosed as rectal cancer after undergoing colonoscopy due to rectal bleeding in May 2018. The pathology report of biopsy tissue indicated moderately differentiated adenocarcinoma (6 cm from the anal verge), with multiple lung metastases observed in the chest CT. Therefore, the clinical stage was determined to be T4N1M1 according to the 2018 NCCN guidelines for colorectal cancer. The patient underwent three cycles of XELOX chemotherapy at another hospital from June to July 2018. In August 2018, he underwent surgical resection of rectal cancer via laparotomy. Postoperative immunohistochemistry results showed CD31 (vascular +), CK20 (+), CK7 (-), D2-40 (lymphatic vessel +), ERCC1 (-), GST-π (+), Ki-67 (approximately 10% +), MLH1 (+), MSH2 (+), MSH6 (+), Mucin-2 (+), P-gp (+), PMS2 (+), Topo-II (sporadic +) and Villin (+). Post-surgical diagnosis was rectal adenocarcinoma and lung metastasis (pT4N-3M1a, stage IV). Thereafter, the patient underwent 10 cycles of targeted therapy with Avastin and XELOX chemotherapy. The treatment was evaluated as Stable Disease (SD) response according to the Response Evaluation Criteria in Solid Tumors (RECIST). From September 6, 2019, to December 19, 2019, the patient received maintenance chemotherapy with Xeloda 1500 mg bid for two weeks and Avastin 500 mg on day 1. From January to May 2020, due to progressive enlargement of lung metastases, disease progression was considered according to the 2020 NCCN guidelines for the diagnosis and treatment of colorectal cancer. The patient received FOLFIRI chemotherapy combined with Avastin (300 mg/kg intravenous infusion every three weeks). The FOLFIRI regimen consisted of irinotecan (Jiangsu Hengrui, National Medical Products Administration approval number H20020687) 130 mg/m^2 on day 1 + calcium folinate (Jiangsu Hengrui, National Medical Products Administration approval number H32022390) 400 mg/m^2 on day 1 + 5-Fu (Tianjin Jinyao, National Medical Products Administration approval number H12020959) 400 mg/m^2 intravenous infusion on day 1 + 5-Fu 1200 mg/m^2 continuous infusion for 48 hours, every three weeks. During the fourth and fifth cycles of chemotherapy in 2020, the patient exhibited a significant increase in blood ammonia levels and corresponding symptoms of encephalopathy. The clinical diagnosis was hyperammonemic encephalopathy. Specific presentation was as follows.

1) During the fourth cycle of chemotherapy, from 16:30 on March 18, 2020 to 17:00 on March 20, 2020, the patient received continuous intravenous infusion of 5-Fu (2 ml/h). The patient developed sluggishness and a significant decrease in appetite from 07:30 on March, which progressed to serious changes at 18:30 on the same day, such as unconsciousness, unresponsiveness, with stiff limbs and no diarrhea. The 5-Fu infusion pump had already completed simultaneously. Physical examination showed dilated pupils with a diameter of about 8 mm, sluggish pupillary light reflex, and increased muscle tone in all limbs. Electrocardiogram monitoring showed blood pressure of 150/85 mmHg, heart rate of 92 beats/min, and blood oxygen saturation of 96%. Rapid fingertip blood glucose was 9.5 mmol/L. Emergency tests showed red blood cells 4.18×10^{12}/L, hemoglobin 129 g/L; blood urea nitrogen 10.7 mmol/L, blood ammonia 117.0 μmol/L, lactate 9.1 mmol/L, alanine aminotransferase 19 U/L; myoglobin 21 ng/ml. Emergency head CT scan showed age-related brain changes, without clear metastases. The clinical diagnosis was hyperammonemic encephalopathy of unknown cause. Treatment at that time included intravenous infusion of aspartate, ornithine injection 60 ml and oral lactulose to promote ammonia excretion after the patient regained consciousness. At 07:30 on March 21, the patient's consciousness returned to normal, with appropriate responses and flexible limb movements. Ammonia was found to be <9 μmol/L on March 21. Subsequent examinations including ultrasound of the portal vein system and liver did not reveal any significant abnormalities. On March 24, the patient refused further examination and requested discharge (a consent form for refusing further examination and automatic discharge was signed).

2) During the fifth treatment cycle from 16:30 on May 11 to 05:30 on May 13, the patient received continuous intravenous infusion of 5-Fu (2 ml/h). On May 12, the patient began to experience an increase in bowel movements, with more than 10 loose stools that day, but did not visit the doctor. At 05:30 on May 13, the patient became unconscious, unresponsive to stimuli and developed stiff limbs. Physical examination showed no abnormalities in heart and lung auscultation, dilated pupils with a diameter of about 8 mm, sluggish pupillary light reflex, and increased muscle tone in all limbs. The 5-Fu infusion pump had 22 ml of liquid left. Electrocardiogram monitoring showed blood pressure of 149/82 mmHg, heart rate of 85 beats/min, and blood oxygen saturation of 98%. Rapid fingertip blood glucose was 8.6 mmol/L. Emergency tests showed no abnormalities in blood routine and coagulation function. Blood urea nitrogen was 8.4 mmol/L, blood ammonia was 349.0 μmol/L, and lactate was 7.6 mmol/L. There were no symptoms of dizziness or vomiting before this chemotherapy. Since the emergency head CT scan from March 2020 showed age-related brain changes without clear evidence of metastases, brain metastases was not considered. However, in emergency situations, head CT scans may be temporarily postponed. The clinical diagnosis at this time was hyperammonemic encephalopathy (not excluding 5-Fu-induced). Treatment: we immediately suspended the infusion of 5-Fu, replaced it with 60 ml of aspartate and ornithine injection intravenously, and performed a vinegar enema. The patient's consciousness gradually improved. At 18:30 on May 14, the patient returned to normal with appropriate responses, and the level of ammonia declined to normal (<9 μmol/L).

Results

The patient experienced severe consciousness disorders during two cycles of 5-Fu chemotherapy, and was clinically diagnosed with hyperammonemic encephalopathy, which was considered to be highly correlated with the continuous infusion of high-dose 5-Fu. The patient's body surface area and drug dosage during five cycles of FOLFIRI chemotherapy are shown in Table 1. The time of onset, symptoms, and recovery time of hyperammonemia during the fourth and fifth cycles of FOLFIRI chemotherapy are presented in Table 2.

Discussion

Elevated blood ammonia, lactate accumulation and the occurrence of hyperammonemic encephalopathy are closely related to the dose and cumulative effect of 5-Fu: The patient was an elderly male who received a total of five infusions of 5-Fu after taking Xylodase (capecitabine) orally for 17 months. During the last two cycles of infusion of 5-Fu, the patient suffered a transient and sharp increase in ammonia, encephalopathy, and significant gastrointestinal reactions. Other drugs used during chemotherapy included intravenous injection of esomeprazole and magnesium isoglycyrrhizinate, oral gabapentin, hydrocortisone sustained-release tablets, and celecoxib. The adverse drug reaction causality assessment, as per the evaluation method of Karch and Lasagna [1] in the 2012 Chinese version of the "Handbook of Adverse Drug Reaction Reporting and Monitoring Work" [2], is categorized into six levels. Based on this assessment, the hyperammonemic encephalopathy observed in this case was deemed to be "definitely" related to 5-Fu. The reasons for the assessment were as follows: (1) There was a clear temporal relationship between the injection of 5-Fu and the onset of patient's symptoms; (2) After discontinuing 5-Fu, the symptoms including consciousness and muscle rigidity improved, as well as the levels of ammonia and lactate; (3) The symptoms recurred after the second infusion of 5-Fu and improved again after stopping the drug; (4) Recent clinical cases have reported a relationship between increased levels of ammonia and lactate with the occurrence of encephalopathy caused by 5-Fu [3,6], which is consistent with known adverse reactions; (5) The symptoms observed in this patient were difficult to explain by other administered drugs or disease conditions.

Characteristics of this case were as follows: Other reported cases have shown that patients developed hyperammonemic encephalopathy after the first or second use of fluoropyrimidine drugs. The onset of hyperammonemic encephalopathy was early and may be related to acute stress or allergic reactions, which would prompt medical staff to reconsider or change the treatment plan earlier. However, the clinical changes occurred after multiple cycles of fluoropyrimidine drugs in this case. Xylodase is an oral drug with relatively no cytotoxicity in vitro. It is converted into 5-Fu in the body through the action of enzymes and exerts its therapeutic effect. The patient had been using Xylodase for 17 months, which was a long treatment cycle, followed by a high-dose intravenous treatment with 5-Fu, which led to the development of hyperammonemic encephalopathy. All of these chemotherapy drugs belong to the same class, and the possibility of dose accumulation effect of 5-Fu cannot be ruled out, which increases the medical risk and should be further explored.

Pathogenic mechanisms of encephalopathy induced by 5-Fu: Long-term use of 5-Fu can lead to neurotoxicity, which is clinically rare. Brain MRI results may explain the manifestation of this type of encephalopathy and can be considered as an indicator of central nervous system toxicity caused by 5-Fu [7]. Most clinical reports of this type of neurotoxicity are delayed, and MRI suggests subacute multifocal leukoencephalopathy, which is considered to be immune-mediated and often occurs when 5-Fu is combined with levomisole [8]. Some scholars performed autopsies on patients who died of hyperammonemic encephalopathy caused by 5-Fu combined with oxaliplatin. MRI showed diffuse brain edema in the bilateral cingulate cortex, while microscopic examination showed spongiform changes in the nervous tissue, increased astrocytosis in the subarachnoid and perivascular regions (perivascular astrocytosis). Clinically, it can manifest as type II dementia [9]. However, this type of brain cortex lesion has not been widely confirmed in such patients.

The reason for encephalopathy is unclear. Yeh [10] proposed two possible mechanisms: deficiency of Dihydropyrimidine Dehydrogenase (DPD) and the influence of 5-Fu metabolites. (1) Approximately 2.7% of patients have been detected with DPD deficiency [11]. DPD is the rate-limiting enzyme for 5-Fu metabolism in the body, and is mainly distributed in the liver and peripheral blood lymphocytes. After 5-Fu enters the blood, about 80% is metabolized and degraded into fluoroacetic acid through the DPD pathway, and the latter is further metabolized into fluoroacetate, with ammonia as the final product. DPD deficiency leads to the accumulation of 5-Fu in the patient's body (without elevated blood ammonia), and high concentrations of 5-Fu can penetrate the cerebrospinal fluid, causing acute myelin sheath degeneration in neurons [10], finally leading to severe neurotoxicity and significant toxic side effects such as gastrointestinal reactions and bone marrow suppression [12]. However, DPD deficiency cannot fully explain 5-Fu-induced encephalopathy. (2) Fluoroacetate-induced encephalopathy is another possible pathogenic mechanism [13]. Okamural [14,15] suggested that the number or function of mitochondria is affected [16,17], and the stability of the tricarboxylic acid cycle can be disrupted when patients have concurrent factors such as renal insufficiency, infection, or muscle loss. Fluoroacetate, as a tricarboxylic acid cycle inhibitor, inhibits the tricarboxylic acid cycle, leading to insufficient ATP synthesis, which in turn causes a disturbance in the ATP-dependent urea cycle, resulting in the inability to convert ammonia, accumulation of blood ammonia in the brain, followed by increased intracranial pressure with cellular edema, finally leading to encephalopathy (Figure 1).

Correlation between reversible hyperammonemia and age-related brain changes, and the occurrence of hyperammonemic encephalopathy

5-Fu is currently the most widely used antimetabolite drug with good efficacy in digestive tract cancer and other solid tumors, and it plays an important role in the treatment. The 5-Fu instructions (all versions) do not describe the elevation of blood ammonia, lactate and encephalopathy caused by 5-Fu, and there are very few domestic and international reports on this topic. Majority of articles associate hyperammonemia with the occurrence of encephalopathy, however not all cases of hyperammonemia lead to encephalopathy.

5-Fu-induced encephalopathy was reported in 1994 due to continuous infusion of high-dose 5-Fu (2600 mg/m^2 per week, continuous infusion for 48 hours) in other countries. Clinical symptoms included confusion, restlessness, hearing impairment, seizures, coma, muscle rigidity, etc., accompanied by hyperammonemia and lactic acidosis. These symptoms generally resolved on their own after drug metabolism or drug treat-

ment [3]. Studies have shown that the proportion of high-dose continuous infusion of 5-Fu leading to elevated blood ammonia is 5.7% (16/280) [3,14]. Liaw [19] reported 32 episodes of hyperammonemic encephalopathy and their clinical characteristics in 29 cancer patients between 1986 and 1998. The onset of related symptoms occurred on an average of 2.6±1.3 days after continuous infusion of 5-Fu (400 mg/m^2 IV on day 1 + 1200 mg/m^2/d continuous infusion for 48 hours, every two weeks). The average blood ammonia concentration was 347.78±239.44 μmol/L, which usually returned to normal levels within 48 hours. Other retrospective studies showed that some patients developed hyperammonemic encephalopathy even with low-dose 5-Fu [4] or oral capecitabine [20]. However, none of the above studies indicated a correlation between the occurrence of hyperammonemic encephalopathy and ammonia levels. Another study has suggested that encephalopathy is likely to occur when ammonia levels reach 96.78 μmol/L, especially when the risk of coma is increased [21]. Since the body can self-regulate, elevated blood ammonia levels are reversible to some extent [22]. Therefore, the occurrence of hyperammonemic encephalopathy in cancer patients may be closely related to the dose and formulation of 5-Fu used, as well as the patient's functional status, such as elderly patients, or patients with age-related brain changes, elderly dementia, and cachexia.

This patient was an elderly male with progressive wasting and age-related brain changes seen on head CT. He was orally taking Xeloda for 17 months. Long-term use of 5-Fu can lead to neurotoxicity [7], which is mostly delayed and clinically rare, but unavoidable. Brain MRI can show similar age-related brain changes, such as subacute multifocal leukoencephalopathy, type II dementia, etc. Hyperammonemia and age-related brain changes may be important factors contributing to the occurrence of hyperammonemic encephalopathy in this patient [23].

Conclusion

This patient's serum DPD level was 34.36 pg/ml by ELISA (reference value 960-3060 pg/ml) [24], indicating a significant deficiency in DPD. The possible reasons for this were as follows:

1) In the early stage of 5-Fu administration, there was no hyperammonemia, but due to the lack of DPD, the continuous administration of 5-Fu and limited metabolism caused rapid accumulation of 5-Fu in the body, which entered the cerebrospinal fluid and caused acute myelinization of neurons, resulting in obvious gastrointestinal toxicity, such as an increase in bowel movements;

2) With the continuous infusion of 5-Fu, the body's DPD metabolic pathway may have negative feedback, and the metabolic products of 5-Fu, such as fluoroacetic acid and fluorocitric acid, inhibit the tricarboxylic acid cycle, leading to a disturbance in the ATP-dependent urea cycle, which prevents ammonia conversion, resulting in the accumulation of blood ammonia in the brain and ultimately leading to the occurrence of hyperammonemic encephalopathy;

3) The patient had previously taken Xeloda orally on multiple occasions and had undergone three cycles of 5-Fu chemotherapy without experiencing hyperammonemic encephalopathy. Hyperammonemic encephalopathy first occurred during the fourth cycle of chemotherapy with the same dosage of 5-Fu, at which point the patient experienced a significant reduction in body weight due to the tumor. According to the above theory, the loss of skeletal muscle in the patient led to a decrease in the number of mitochondria and damage to the tricarboxylic acid cycle, which may also explain the increase in ammonia due to the disturbance of the urea cycle.

This study suggested that:

(1) Although the mechanism of 5-Fu-induced hyperammonemic encephalopathy is unclear, there are numerous clinical studies on the safety of 5-Fu usage [25,26]. For patients with DPD deficiency, elderly, progressive wasting and metabolic disorders, drug dose reduction or the use of alternative drugs should be considered.

(2) There are differences in the metabolism of 5-FU in different individuals, and the method of determining the dosage based on body surface area cannot meet the clinical needs of drug use. The method of calculating the dosage for this drug is not the optimal choice. For instance, although the patient's weight loss resulted in changes in body surface area, there was no significant difference in the dosage calculated based on body surface area in recent five cycles of chemotherapy. However, due to the altered tolerance, obvious adverse reactions occurred. In such special patient populations, Therapeutic Drug Monitoring (TDM) can be considered to monitor blood drug concentration and guide the 5-Fu dosage. This calculation, combined with the patient's weight, infection status, etc., significantly improves the objective response rate of patients with advanced colorectal cancer and reduces adverse reactions [27]. Currently, individualized dosing of 5-Fu based on pharmacokinetics in clinical applications is being investigated in Europe and the United States, which has not yet been included in the guidelines for the use of drugs in cancer patients.

(3) In clinical practice, if conditions permit, it is recommended to conduct a comprehensive evaluation of the patient's physical condition before chemotherapy, including DPD testing, head MRI plain scan, liver and kidney function tests, weight, and other indicators, to avoid the use of 5-Fu in cases of infection or dehydration. This clinical report discusses important implications for the selection of clinical treatment plans and the overall management of cancer patients.

Key findings

• The patient had underwent about 20 months of fluorouracil drugs of chemotherapy before he developed to hyperammonemic encephalopathy, with no significant change in his Body Surface Area (BSA).

What is known and what is new?

• Here is known: There are two possible mechanisms resulted in the occurence of the remarkable side, including dihydropyrimidine dehydrogenase (DPD) deficiency as well as disruption of tricarboxylic acid cycle stability.

• Here is new: These two pathogenic mechanisms may exsit at the same time in this case.

What is the implication, and what should change now?

• For patients with DPD deficiency, elderly, progressive wasting and metabolic disorders, drug dose reduction or the use of alternative drugs should be considered.

• Therapeutic Drug Monitoring (TDM) can be considered to monitor blood drug concentration and guide the 5-Fu dosage.

• It is recommended to conduct a comprehensive evalua-

tion of the patient's physical condition before chemotherapy to avoid the use of 5-Fu in cases of infection or dehydration.

Declarations

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee (s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Author contributions:

(I) Inception and design: S Jin, J Zhang;

(II) Administrative support: J Zhang;

(III) Provision of study materials or patients: S Jin;

(IV) Collection and assembly of data: S Jin, C Dai, W Cai;

(V) Data analysis and interpretation: S Jin, C Dai, W Cai,W Bai;

(VI) Manuscript writing: All authors;

(VII) Final approval of manuscript: All authors.

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