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A RARE PRESENTATION OF 5-FLUOROURACIL(5FU) INDUCED CEREBRAL ENCEPHALOPATHY

Oncology

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ABSTRACT

5-Fluorouracil (5FU), is a commonly used antimetabolite and antineoplastic agent, has been approved for the treatment of various cancers, since its introduction in 1957. It is associated with systemic side effects such as gastrointestinal problems, neutropenia etc. 5-FU induced encephalopathy is very rarely reported. It is mainly a diagnosis of exclusion of the other causes in case of first episode of seizure. Hyperammonemic encephalopathy is a rare adverse effect following continuous intravenous infusion of 5-FU chemotherapy manifesting as altered mental status with elevated ammonia levels with no radiologic abnormality. We report one case of 5-FU induced hyperammonemic encephalopathy, who presented with confused mental status with no other systemic abnormality in background, after FLOT (5-FU, Leucovorin, Oxaliplatin, Taxane) chemotherapy regimen in a case of locally advanced gastric adenocarcinoma.

KEYWORDS

5-Fluorouracil, Hyperammonemic encephalopathy, Fluoropyrimidine, Antimetabolite, 5-fluoro-2-deoxyuridine-5-phosphate, FLOT regimen, thymidylate synthase enzyme, generalised tonic clonic seizure, Myelosuppression, Hand foot syndrome (palmer-planter-erythrodysesthesia, Glasgow Coma Scale, Thiamine pyrophosphate (TPP), Dehydropyrimidine dehydrogenase (DPD).

INTRODUCTION

5-FU is a fluoropyrimidine analog with cell cycle specificity in the S phase. This anti-metabolite is used to treat variety of cancers such as colorectal, breast, GI malignancies, head and neck malignancies. The activated cytotoxic metabolite form(5-fluoro-2-deoxyuridine-5-phosphate) inhibits thymidylate synthase enzyme and is incorporated into DNA and RNA, resulting in inhibition of DNA and RNA synthesis. The common side effects of 5-FU are related to its effects on the gastrointestinal tract and bone marrow. The symptoms include bone marrow suppression, nausea, vomiting, diarrohea, stomatitis. 5-FU induced neurotoxicity is rare. Here is a report on a patient who developed acute neurotoxicity and hyperammonemia after systemic chemotherapy with a continuous infusion of 5-FU as a part of FLOT regimen.

CASE

A 35 years old male was planned for curative radical total gastrectomy for his locally advanced gastric cancer along with perioperative chemotherapy with FLOT regimen (5FU 2600 mg/m^2 iv infusion over 24 hours, Leucovorin 300 mg/m^2 iv over 2 hours, Oxaliplatin 85 mg/m^2 iv over 2 hours, Docetaxel 85 mg/m^2 iv over 2 hours on day 1 x 2 weekly). Whole chemotherapy infusion period was uneventful. He developed one episode of generalised tonic clonic seizure with tongue bite, eye ball rolling upwards followed by post ictal confusion state. He was sedated because of aggressive behaviour. There was no past history of seizure disorder. After that the patient became disoriented. Initial CBG and ABG value was normal, B.P was low, no electrolyte imbalance, no meningeal irritation sign, afebrile, total count was high (22860), serum urea was high. All other vital signs and blood parameters are within normal limit. The patient remained disoriented occasionally comatose, with poor GCS (9/15) for three days. After three days GCS improved but he remained agitated, restless, and aggressive. Neurologic examination after the GTCS revealed decreased higher function, normal pupillary reflex, normal superficial and deep tendon reflexes except non responsive right plantar and extensor left plantar reflex. Initial CECT Brain shows no active bleeding or structural abnormality. MRI Brain could not be done at first due to excessive restlessness of this patient. The patient was shifted to High dependency unit for intensive care. The patient was on empirical antiviral, antibacterial, anticonvulsant therapy. His blood ammonia level was borderline (85 ug/dl- normal value upto 90 ug/dl), plasma lactate value was normal. A MRI Brain was done after proper sedation, which shows no structural abnormalities. Other laboratory tests provided no explanation for his symptoms. Neuromedicine specialist did not opine for CSF study as there was no meningeal irritation sign, no fever. The patient was treated with a lactulose retention enema. The patient's symptoms including the neuropsychiatric problems, high total count, high serum urea were recovered over a 10 days span. After this incident, his chemotherapy regimen was changed which went uneventful. At present he has completely recovered after treatment and is prepared for his upcoming surgery.

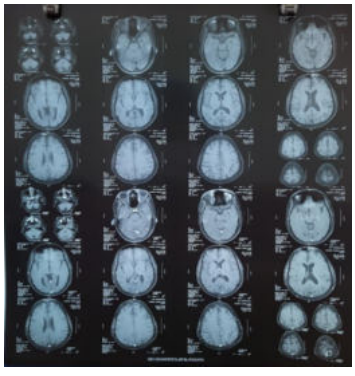

Fig 1 CECT BRAIN (Post Chemotherapy)

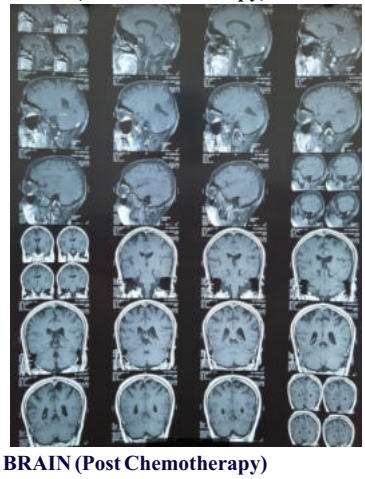

Fig 2 CECT BRAIN (Post Chemotherapy)

DISCUSSION

5-FU, was first synthesized in 1957, which is currently one of the most widely used anti-cancer, anti-metabolic agents as it shows activity against a broad range of solid tumors, including gastrointestinal, breast and head and neck cancer. The spectrum of 5-FU's toxicities are both dose and schedule-dependent (1). It acts on rapidly dividing tissues, and specifically the gastrointestinal mucosa and bone marrow. Myelosuppression is schedule-dependent, when administering 5-FU as a bolus. The gastrointestinal tract toxicity is characterized by epithelial ulceration such as mucositis, esophagitis, gastritis and colitis with diarrhoea, nausea, vomiting. These symptoms are well controlled with antiemetics. The other toxicities associated with 5-FU therapy include dermatologic toxicities such as alopecia and fingernail changes, Hand foot syndrome(palmer-planter-erythrodysesthesia) and uncommonly cardiotoxicity. Neurotoxicity is one of the rare adverse effects associated with 5-FU treatment. The acute and delayed forms of 5-FU related neurotoxicity have been reported (2). The acute form consists of cerebellar syndrome and encephalopathy which are reversible upon drug discontinuation, whereas the delayed variety takes the form of subacute multifocal leukoencephalopathy.

Although some theories have been proposed, the mechanisms for the neurotoxicity of 5-FU. Some researchers believe that accumulated fluoroacetate, which is a product of 5-FU catabolism that inhibits the Krebs cycle enzyme, leads to impairment of the urea cycle (3). According to this theory, ammonia, which is a product of 5-FU metabolism, accumulates in large amounts after the administration of high dose 5-FU. Therefore, encephalopathy subsequently occurs and accompanied by hyperammonemia and lactic acidosis. Kim et al. have reported on a case for which an intermediate dose of 5-FU induced encephalopathy (4). Using real-time PCR, the patient's mRNA level of DPD enzyme was checked before and after treatment and this was compared with those levels of a control group of 16 patients who were treated with the same regimen. The results showed that the patient's pre-treatment level of DPD was in the control range, but its level was elevated up to 187% after 5-FU treatment. According to their results, the authors suggested that the transient stagnation of 5-FU's catabolites would play an important role in the development of neurotoxicity. Another theory to explain the neurologic adverse effect by 5-FU therapy is that this drug causes deficiency of thiamine. Thiamine pyrophosphate (TPP) is the active form of the vitaminB1. Exposure to 5-FU can increase the TPP level. These results indicate that 5-FU may increase the cellular thiamine metabolism, and this can possibly exacerbate thiamine deficiency (5). This theory is supported by the fact that the symptoms of the Wernicke-Korsakoff syndrome, including ataxia, nystagmus, mental confusion and cognitive changes, are similar to the neurotoxic effects of fluorouracil.

Dehydropyrimidine dehydrogenase (DPD) is a breakdown enzyme of 5-FU, and DPD is distributed in the liver, gastrointestinal mucosa and peripheral lymphocytes. More than 80% of the administered 5-FU is catabolized by DPD (6). Thus, a deficiency of this enzyme can cause fatal toxicity when a patient is treated with fluoropyrimidine-based chemotherapy (2). The incidence of DPD deficiency in cancer patients has been estimated to be 2.7%, and this can be accompanied by severe fluorouracil toxicity (7).

The diagnosis of 5-FU related encephalopathy is diagnosis of exclusion: (1) the development of encephalopathy during or shortly after the completion of 5-FU administration, (2) exclusion of other metabolic factors that may affect a patient's consciousness and mental functioning, such as hypoglycemia, organ failure, electrolyte imbalance, sepsis, (3) and central nervous system involvement by cancer, and (4) exclusion of an adverse effect by concomitant medications (8).

The patient in this study experienced a sudden onset of generalised tonic clonic seizure for about two minutes followed by post-ictal confusion and coma,1day after the first cycle of chemotherapy treatment. GCS improved after three days associated with agitation, restlessness and aggressiveness. The laboratory findings showed increased total count, increased serum urea, borderline serum ammonia level yet this problem was corrected with appropriate fluid therapy, empirical antibiotics, antiviral, anticonvulsant, lactulose retention enema. Radiology shows no structural abnormality or intracranial bleeding. Most of the 5-FU-associated neurotoxicities developed during 5-FU infusion, or shortly after completion of the 5-FU infusion. However, some previous studies have reported on symptoms that were expressed within a few days to five weeks after treatment (9), so that we can speculate on the notion that his symptoms could have been caused by chemotherapy-related side effects. The serum ammonia level was borderline. Although we were not able to check the level of decreased DPD activity, we indirectly suspected he had a DPD enzyme deficiency according to his clinical symptoms. We thought that the cause of the neurotoxicity in this patient was the reduced level of DPD enzyme, and we stopped using the previous regimen, including the 5-FU, and we started conservative treatment for the encephalopathy such as fluid supplementation, i.v mannitol, antibiotics, antiviral, anticonvulsant, iv steroids, a lactulose enema (4,10). His symptoms then recovered in ten days.

Some reports on DPD deficiency confirmed this condition by performing DPD enzyme assay with using peripheral blood mononuclear cells (7,11), or by assessing the low mRNA levels of DPD enzyme, as estimated by real-time quantitative PCR (12). However, DPD deficiency has a low incidence, and if it is suspected, then a quick break in the medication, along with conservative treatment, can result in a recovery from symptoms.

In conclusion, physicians should take notice of the neurological symptoms of cancer patients who are being treated with 5-FU-based chemotherapy.

REFERENCES

1. Grem JL. 5-Fluorouracil: forty-plus and still ticking. A review of its preclinical and clinical development. Invest New Drugs. 2000;18:299–313.
2. Pirzada NA, Ali II, Dafer RM. Fluorouracil-induced neurotoxicity. Ann Pharmacother. 2000;34:35–38.
3. Koenig H, Patel A. Biochemical basis for fluorouracil neurotoxicity. The role of Krebs cycle inhibition by fluoroacetate. Arch Neurol. 1970;23:155–160.
4. Kim YA, Chung HC, Choi HJ, Rha SY, Seong JS, Jeung HC. Intermediate dose 5-fluorouracil-induced encephalopathy. Jpn J Clin Oncol. 2006;36:55–59.
5. Heier MS, Dornish JM. Effect of the fluoropyrimidines 5-fluorouracil and doxifluridine on cellular uptake of thiamin. Anticancer Res. 1989;9:1073–1077.
6. Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB. Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. Cancer Res. 1987;47:2203–2206.
7. Etienne MC, Lagrange JL, Dassonville O, Fleming R, Thyss A, Renee N, et al. Population study of dihydropyrimidine dehydrogenase in cancer patients. J Clin Oncol. 1994;12:2248–2253.
8. Yeh KH, Cheng AL. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. Br J Cancer. 1997;75:464–465.
9. Cho IJ, Chang HJ, Lee KE, Won HS, Choi MY, Nam EM, et al. A case of Wernicke's encephalopathy following fluorouracil-based chemotherapy. J Korean Med Sci. 2009;24:747–750.
10. Cheung WY, Fralick RA, Cheng S. The confused cancer patient: a case of 5-fluorouracil-induced encephalopathy. Curr Oncol. 2008;15:234–236.
11. Takimoto CH, Lu ZH, Zhang R, Liang MD, Larson LV, Cantilena LR, Jr, et al. Severe neurotoxicity following 5-fluorouracil-based chemotherapy in a patient with dihydropyrimidine dehydrogenase deficiency. Clin Cancer Res. 1996;2:477–481.
12. Baek JH, Kim JG, Kim SN, Kim DH, Sohn SK, Hong YJ, et al. Unpredicted severe toxicity after 5-fluorouracil treatment due to dihydropyrimidine dehydrogenase deficiency. Korean J Intern Med. 2006;21:43–45.