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5-Fluorouracil-Induced Hyperammonemia Encephalopathy in a Patient with Gastric Cancer

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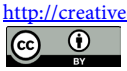


Abstract

Chemotherapy with 5-fluorouracil (5 FU) has been widely used to treat advanced gastric cancer. Knowing the side effects is therefore important in order to better prevent them. Fluoropyrimidine-induced hyperammonemic encephalopathy is a rare complication and characterized neurological status with elevated ammonia level without radiological abnormalities. We report the first case of 5 FU-induced hyperammonemic encephalopathy in women patients on induction chemotherapy for gastric cancer in Madagascar. His ammonia level (NH_3) was 102 µmol/l. The patient recovered from his confusional state after two days of treatment with hyperhydration and vitamin therapy.

Keywords

Encephalopathy, Gastric Cancer, Hyperammonemia, 5-Fluororuracil

1. Introduction

Gastric cancer ranks fifth in terms of incidence and fourth in terms of cancer-related deaths worldwide [1]. In Madagascar, gastric cancer is uncommon according to some hospital data [2] [3]. Nearly 50% of patients present at an advanced stage and up to 80% of patients have lymph node metastases at diagnosis. The prognosis of gastric cancer remains poor. The overall 5-year survival rate for gastric cancer is less than 50% [4]. Neoadjuvant chemotherapy has become the standard of care for resectable locoregional gastric cancer [5]. FLOT (5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel) chemotherapy is associated with

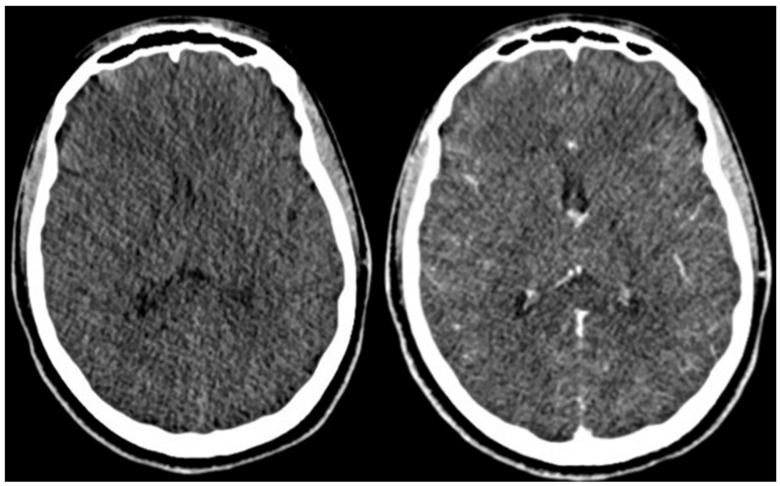
significantly higher overall survival than ECF (Epirubicin, Cyclophosphamide, 5-Fluorouracil) and a higher R0 resection rate [5]. The main side effects of this protocol are diarrhoea, leuko-neutropenia, infection and peripheral neuropathy. Hyperamonemic encephalopathy related to 5-FU infusion is a rare complication and could be fatal. The pathophysiology remains unclear. The incidence of hyperammonemic encephalopathy varies between 0.6% and 8.7% depending on the dose of 5-FU [6]. To our knowledge, we report the first case of 5 FU-induced hyperammonemic encephalopathy in a patient on induction chemotherapy for gastric cancer in Madagascar.

2. Case Report

46 year-old-woman referred to the oncology department in June 2022 for gastric adenocarcinoma of the cardia with lymph node involvement. The patient is a non-smoker with no comorbidities. The physical examination showed a patient in fairly good general condition, body mass index 19, without fever. The rest of the examination was unremarkable. The extension work-up, including a thoracic-adbomino-pelvic scan, did not reveal any secondary location. The case was discussed at a multidisciplinary consultation meeting, and three courses of neoadjuvant chemotherapy of the FLOT type (5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel) followed by surgery for excision and then adjuvant chemotherapy were approved. Pre-therapy work-up was normal. The blood count showed a haemoglobin of 10 g/l, a leukocytosis of 9500/mm^3 with a neutrophil of 6005/mm^3; creatinine level of 1 mg/dl with a creatinine clearance of 88.9 ml/min. The liver tests are normal. The patient had received his first course of chemotherapy with Docetaxel 50 mg/m^2, Leucovorin 50 mg/m^2, Oxaliplatin 85 mg/m^2 on the first day and 5-FLuorouracil 2000 mg/m^2 infused over 24 hours. On the first day, the patient was nauseous and vomiting. On the second day, during the 5-Fluorouracil infusion, the patient was confused and agitated. Vital parameters were normal. Neurological examination revealed a Glasgow score of 11 on a scale of 15 (Eye opening 2 of 4, Verbal response 3 of 5, and Motor response 6 of 6). The patient had no sensory or motor deficits. Lung, heart and abdominal examinations were unremarkable. The patient had no signs of dehydration. The emergency biology work-up revealed a lysis syndrome (**Table 1**).

The emergency brain scan was normal; there were no suspicious-looking brain lesions or cerebral oedema (**Figure 1**).

The electroencephalogram (EEG) showed no abnormal tracings. The patient was hydrated with saline 2 L per day combined with B-complex vitamins four ampoules per day. On the second day of treatment, the neurological state improved. By the fourth day, consciousness had returned to normal and the ammonia value had dropped to 55 µmol/L. A reduction in the dose of 5-fluorouracil to 50% was carried out for the next two chemotherapies. The patient did not develop a neurological disorder and was able to complete her neoadjuvant treatment.



(a) (b)

Figure 1. Axial section of a cerebral CT scan without injection (a) the after injection of contrast (b), showing no cerebral abnormality.

Table 1. Major laboratory findings of the patient during encephalopathy.

	Reference	During encephalopathy
NH_3 (µmol/l)	**0 - 55.6**	**102**
Uric acid (µmol/l)	130 - 360	854
Magnesium (mmol/l)	0.7 - 1.1	0.43
Calcium (mmol/l)	2.20 - 2.60	2.19
Créatinine (mg/dl)	0.5 - 1.4	1.4
ALAT/ASAT (UI/L)	5 - 36/13 - 34	22/33
Na (mmol/l)	133 - 145	150
K (mmol/l)	3.5 - 5	5

ASAT: Aspartate aminotransferase, ALAT: Alanine aminotransferase, K: Potasium Na: Sodium.

3. Discussion

Intravenous 5 FU induces severe toxicities in 10% - 40% of patients depending on the protocol, and lethal toxicities in 0.2% - 0.8% of patients [7]. The diagnosis of 5 FU-induced encephalopathy was retained after eliminating all other causes of disturbance of consciousness [6]. Encephalopathy can occur during the first exposure to the drug as in our case. Encephalopathy frequently develops with high dose 5 FU of 1800 to 2600 mg/m^2 over 24 hours and also at the intermediate dose of 1000 mg/m^2 per 24 hours [8]. Our patient had received an infusion of 2000 mg/m^2 over 24 hours. The time of onset may occur during or after the infusion with an average interval of 2 - 6 days [8]. In this case, the neurological signs occurred during the 5-FU infusion. According to a French study, the severity of the neurological state could be related to the value of the ammomia [9].

In our patient, the ammonia was not very high 102 µmol/l and the Glasgow score was 11 on a scale of 15. The pathophysiology is unclear but two mechanisms may explain this symptomatology. Firstly, inhibition of the Krebs cycle by high dose 5-FU administration which induces accumulation of fluoroacetate and directly inhibits the Kreb cycle [7]. Secondly, dihydropyrimidine dehydrogenase (DPD) deficiency which led to inactivation of 5 FU. High concentrations of 5 FU in DPD deficiency enter the cerebrospinal fluid and cause acute demyelination of neurons [6]. DPD deficiency is reported in 2.7% of cancer patients and is thought to be due to a mutation in the DPD gene encoding the DPD enzymes. In our case, we were unable to confirm the presence of DPD deficiency as this test is not available in Madagascar.

Several factors favour hyperammonemic encephalopathy such as infection, dehydration, constipation and renal failure [10]. Our patient had presented with vomiting. There is therefore a possibility that dehydration favoured the development of encephalopathy although there are no obvious signs on physical examination.

The use of uridine triacetate, an antidote to 5 FU, has become a standard in the management of severe 5-FU toxicity in developed countries [11]. Extracorporeal dialysis may be indicated in the presence of severe hyperammonia [9]. In our patient, the ammonia was not very high. Discontinuation of the 5 FU infusion combined with hyperhydration resulted in recovery of the neurological status and a decrease in serum ammonia.

The reintroduction of 5 FU could be achieved with a 50% reduction in dose as was our case. However, dose reduction may limit the effectiveness of treatment. It is therefore important to correct risk factors and, if possible, to look for DPD deficiency before reintroducing 5-FU to better prevents the effects of the treatment.

4. Conclusion

Clinical surveillance is required when administering 5-FU therapy, especially to patients with aggravating factors for encephalopathy. The establishment of a molecular biology laboratory in Madagascar would allow the detection of DPD deficiency and the prevention of serious complications related to 5-Fluorouracil.

Conflicts of Interest

The authors declare no conflicts of interest.

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