CASE REPORT

5-Fluorouracil–induced Encephalopathy in a 51-year-old Man

AS Lee, TW Leung, FCS Wong, WK Sze, SY Tung, SK O
Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong

ABSTRACT
A case of hyperammonaemic encephalopathy that developed during the administration of a widely used chemotherapy regimen is reported in a 51-year-old man. 5-Fluorouracil was considered to be the causative agent. Although encephalopathy is a rare toxic effect of 5-fluorouracil, this case illustrates a serious and potentially life-threatening complication during a chemotherapy regimen using 5-fluorouracil. If patients develop unexplained changes in mental status during intravenous infusion of high-dose 5-fluorouracil, hyperammonaemic encephalopathy should be considered, and chemotherapy should be discontinued immediately. The plasma ammonia level, arterial blood gas content, and plasma lactate level should be measured.

Key Words: Ammonium compounds/blood; Brain diseases/chemically induced; Fluorouracil/adverse effects; Infusions, intravenous

INTRODUCTION
5-Fluorouracil (5FU) is a commonly used chemotherapeutic agent in many chemotherapy regimens. High-dose infusion of 5FU with cisplatin (the PF regimen) is commonly used to treat head and neck cancers as well as cancers of the upper gastrointestinal tract. The regimen is generally well tolerated, and the main toxic effects are myelosuppression and mucositis. Neurotoxicity may occasionally occur, either in the form of cerebellar dysfunction or, very rarely, encephalopathy. This report describes a case of encephalopathy in a patient who received the PF regimen.

CASE REPORT
A 51-year-old man with nasopharyngeal cancer who was treated with radical external radiotherapy 10 years previously developed regional lymph node relapses in 2001 and 2002. The relapses were treated with radical neck dissection, brachytherapy, local excision, and small-field radiotherapy. He subsequently presented to the Department of Clinical Oncology at Tuen Mun Hospital with another lymph node recurrence in the left supraclavicular region. He was scheduled for palliative chemotherapy with the PF regimen — namely, cisplatin 100 mg/m² on day 1 and 5FU 1 g·m⁻²·d⁻¹ as a continuous intravenous infusion from days 1 to 5.

In the early morning of the third day of chemotherapy, the patient was noticed to be drowsy. His level of consciousness subsequently decreased. Although there was spontaneous eye opening, no verbal or motor responses were detected. Chemotherapy was stopped. Clinical examination revealed slight asymmetry in pupil size. The muscle tone of all 4 limbs increased and jerks were brisk. There was no fever and no neck rigidity. Blood investigations revealed an elevated international normalized ratio, at 1.5. The plasma ammonia level was 99 µmol/l (normal range, 16 to 60 µmol/l). Arterial blood gas investigations showed metabolic acidosis and marked hypocapnia. No major electrolyte imbalance was found. The spot glucose level was unremarkable. Plain computed tomography scans of the brain showed no abnormality. Magnetic resonance imaging of the brain, however, revealed small areas of bilateral temporal necrosis.

Supportive treatment (including close monitoring of vital signs and administration of intravenous fluid, oxygen, antibiotic, lactulose, and neomycin) was given. The patient recovered fully the next day. There were no residual neurological deficits. Levels of liver enzymes
were not increased since presentation. The international normalized ratio became normal the next day, as did the plasma ammonia level. There was no significant bone marrow suppression or mucositis related to the course of chemotherapy. The patient was subsequently given another chemotherapy regimen (gemcitabine plus cisplatin), and he tolerated the treatment well. In consideration of the clinical picture and laboratory findings, the diagnosis was 5FU-induced hyperammonaemic encephalopathy.

DISCUSSION

Acute hyperammonaemic encephalopathy has been reported when 5FU was given in a high-dose infusion. The condition is characterised by an abrupt alteration in mental status and an elevated plasma ammonia level in the absence of obvious liver disease. Yeh reported that in addition to hyperammonaemia, lactic acidosis and hypocapnia occur in parallel in the development of encephalopathy. Hypocapnia was also detected in the patient in the present report, but the plasma lactate level was not measured.

Apart from 5FU-induced hyperammonaemia, the differential diagnoses in this patient may include cisplatin-induced encephalopathy and dihydropyrimidine dehydrogenase deficiency. Although cisplatin induces mainly a peripheral sensory neuropathy, cisplatin-induced encephalopathy has been reported in the literature. Cisplatin was also administered before the onset of encephalopathy in this patient. It is, however, unlikely to be the main contributor to the encephalopathy in this case, given the absence of complications when it was administered subsequently with gemcitabine. Dihydropyrimidine dehydrogenase deficiency as a differential diagnosis is also unlikely in this case, given the absence of significant bone marrow suppression or mucositis.

The onset of 5FU-induced encephalopathy may range from 0.5 to 5 days. The median time has been reported to be 19.5 hours from the commencement of high-dose 5FU infusion. The spectrum of encephalopathy may include disorientation, confusion, agitation, neurosensory hearing impairment, seizure, stupor, and deep coma. The majority of patients have severe symptoms of stupor or coma. The median duration of encephalopathy between discontinuation of 5FU infusion and complete recovery is 15 hours (range, 3 to 72 hours).

In the patient in this report, both the onset time and recovery time were well within these ranges.

The exact mechanism of transient hyperammonaemia is uncertain. Yeh and Cheng postulated that hyperammonaemia was due to rapid accumulation of a large amount of ammonia — an end-product of 5FU — together with inhibition of the Kreb’s cycle, which is normally responsible for ammonia clearance, by an intermediate metabolite of 5FU. On the other hand, Lukaschek et al suggested that neurotoxicity (as well as cardiotoxicity) is related to degradation compounds in certain 5FU formulations.

The incidence of 5FU-induced encephalopathy in patients receiving high-dose continuous 5FU infusion was 5.7% in one series. Pre-renal azotaemia and infection were found to be the predisposing factors. Malnutrition and associated thiamine deficiency are also said to contribute to this syndrome. Although there is no evidence that thiamine supplementation can reverse the condition, one report suggested that steroids and thiamine may expedite neurological recovery. It is not known, however, whether pre-existing neurological abnormalities, such as temporal lobe necrosis in this case, will predispose to encephalopathy. Cisplatin was included in the regimen in some of the previous reported cases of 5FU encephalopathy, but there has so far been no evidence to suggest the potentiation of 5FU neurotoxicity by cisplatin.

There is no specific treatment or antidote for hyperammonaemic encephalopathy. The most important measure is to discontinue the 5FU infusion immediately. General supportive care should also be offered. Any underlying predisposing factors such as dehydration and infection need to be corrected. The plasma ammonia level may be lowered by decreasing ammoniagenic substrates with lactulose, giving enemas, and restricting dietary protein intake, as well as inhibiting ammonia production in the gut by giving neomycin enterally. Fortunately, most patients recover completely. From the available literature, the overall rate of complete recovery is approximately 93%. One patient reportedly had residual bilateral neurosensory hearing impairment. Mortality from this condition has occurred, and 3 deaths have been reported in the literature.

Regarding the spectrum of neurotoxicites of 5FU, apart from the commonly described acute cerebellar syndrome and the rare encephalopathy exemplified in this case, there have also been reports of delayed neurotoxicity, in the form of subacute multifocal leukoencephalopathy, which occurred when 5FU was given in combination with levamisole.
CONCLUSION
If patients develop unexplained changes in mental status during intravenous infusion of high-dose 5-fluorouracil, hyperammonaemic encephalopathy should be considered, and chemotherapy should be discontinued immediately. The plasma ammonia level, arterial blood gas content, and plasma lactate level should be measured.

REFERENCES