CASE REPORT

5-FU-induced leukoencephalopathy with reversible lesion of splenium of corpus callosum in a patient with colorectal cancer

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SUMMARY

5-Fluorouracil (5-FU), a commonly used antimetabolite and antineoplastic agent, has been approved for treatment of various cancers. Neurotoxicities are considered extremely rare side effects of 5-FU. We present a case of 5-FU-induced encephalopathy with diffusion-restricted reversible lesion of the splenium of the corpus callosum in a patient with colorectal cancer. The patient presented with confusion, dysarthria and agitation after 5-FU infusion. The prognosis of this toxic effects of 5-FU is usually good if recognised and treated in time. Emergency physicians, general practitioners and oncologists should be aware of this rare side effects of 5-FU chemotherapy and its diagnosis and treatment.

BACKGROUND

5-fluorouracil (5-FU), a commonly used antimetabolite and antineoplastic agent, has been approved for treatment of various cancers. Common adverse effects of 5-FU therapy include myelosuppression, nausea, vomiting, diarrhoea, mucositis and hand-foot syndrome. Acute encephalopathy is a rare neurotoxicity of 5-FU, and only a few case reports have been published in the English literature. 5-FU-induced encephalopathy is often associated with a MRI-identifiable lesion in the brain. The characteristic findings are diffuse and include high-signal intensity in the deep cerebral white matter and corpus callosum on T2-weighted images.

We present a case of acute leukoencephalopathy with a unique reversible lesion on the splenium of the corpus callosum in the brain of a patient with colorectal cancer being treated with folinic acid leucovorin, 5-FU, irinotecan (FOLFIRI) plus bevacizumab.

CASE PRESENTATION

A 67-year-old man with a history of stage IV colorectal cancer presented to the emergency department (ED) of a comprehensive cancer centre with confusion, dysarthria and agitation. A family member reported that the patient had begun to exhibit intermittent confusion and dysarthria the previous evening. The patient was profoundly confused, agitated, dysarthric and ataxic the following morning and was brought to the ED. There was no history of fever, head injury, previous or current witnessed seizure, smoking or use of alcohol or illicit drugs. Nausea and vomiting were

reported to have occurred intermittently since the start of chemotherapy. The patient had a medical history of mild chronic kidney disease (stage 2, baseline creatinine 1.2 mg/dL), cardiomyopathy with a left ventricle ejection fraction of 48%, metastatic colorectal cancer with no evidence of brain metastasis, and pulmonary embolism. The patient's medication list included carvedilol, lisinopril, ondansetron and prochlorperazine.

The patient had been diagnosed 8 months previously with colorectal adenocarcinoma metastasized to the liver. After having received three cycles of FOLFOX plus bevacizumab, the patient was switched to FOLFIRI/bevacizumab due to his complicated clinical course and evidence of disease progression. There was a significant time lapse (2.5 months) between ending FOLFOX/bevacizumab and beginning FOLFIRI/bevacizumab because the patient suffered from various medical conditions that prevented him from starting the new chemotherapy regimen.

Two days before presenting to the ED, the patient received his first cycle of leucovorin 400 mg/m², 5-FU 400 mg/m², irinotecan 180 mg/m² and bevacizumab 450 mg. He then underwent a 46-hour continuous infusion of 5-FU 2400 mg/m². The patient presented to the ED 3 hours after completing this continuous 5-FU infusion.

INVESTIGATIONS

In the ED, the patient's triage vitals were heart rate 120 beats/min, respiratory rate 18 breaths/min, blood pressure 121/82 mm Hg, temperature 98.8°F and oxygen saturation 100% on room air. The patient was confused, dysarthric and highly agitated. He was able to follow simple commands but not respond to questions. Initial blood work showed elevated levels for blood urea nitrogen (BUN) 22 mg/dL (normal range 8–20 mg/dL), creatinine 1.47 (normal range 0.7–1.3 mg/dL), bilirubin (total bilirubin 2.8 mg/dL (normal range 0.2–1.3 mg/dL); indirect bilirubin 2.6 mg/dL (normal range 0.0–1.1 mg/dL)) and lactic acid 5.5 mmol/L (normal range 0.9–1.7 mmol/L). Complete blood count, serum electrolytes, glucose, ammonia, thiamine, blood pH and liver enzyme results were normal except for elevated INR 2.64 (therapeutic range 2.0–3.0; the patient was taking coumadin for pulmonary embolism), mild hypokalaemia 3.3 mEq/L (normal range 3.5–5.0 mEq/L)

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Figure 1 Multisequence MRI of brain without intravenous contrast showing subtle increased T2/fluid-attenuated inversion recovery hyperintensity in the splenium of the corpus callosum annotated with an arrow in (A) and (B). The same area shows the restricted diffusion indicated by hypointensity on apparent diffusion coefficient maps on (C).

and hypomagnesaemia 1.6 mg/dL (normal range 1.8–2.3 mg/dL). Other systemic examination results were within normal range. Chest X-ray and CT head were negative. Bedside EEG showed diffuse disturbance of cerebral activity, with no seizure activity. The patient was admitted to the hospital. A diffusion-weighted (DW)-MRI brain scan showed a diffusion-restricted lesion in the splenium of the corpus callosum (figure 1). The patient was on coumadin and had elevated INR, so lumbar puncture (LP) was delayed. Subsequently, LP was not done as the patient had a rapid reversal of neurological functions and lacked the signs of infection. Cerebrospinal fluid analysis can help in ruling out central nervous system infections such as herpes encephalitis if clinically deemed.

DIFFERENTIAL DIAGNOSIS

Toxic, metabolic, septic (including central nervous system infection), hepatic and uraemic encephalopathy are known differentials of the acute encephalopathy. Sometimes, a patient with a non-convulsive seizure may present with the acute confusional state. Drugs, toxins or medications are a frequent cause of toxic metabolic encephalopathy. Electrolyte imbalances, hypoglycaemia/hyperglycaemia, thiamine deficiency, acidosis, hypoxaemia and organ failure such as renal or hepatic failure are known to cause acute encephalopathy. Non-convulsive seizures may also present with altered mental status. A careful review of the patient's medications helps in diagnosis of toxic encephalopathy. A previous study has reported a case with 5-FU-induced leukoencephalopathy with an acute stroke-like presentation,¹ which suggests the difficulty in diagnosis of 5-FU-induced leukoencephalopathy in the acute phase.

TREATMENT

He received intravenous hydration, antibiotics and haloperidol (5 mg), diphenhydramine (25 mg) and chlorpromazine (25 mg) during the ED stay in an attempt to control his agitation.

OUTCOME AND FOLLOW-UP

The patient's mental status improved to baseline within 24 hours of his presentation to the ED with intravenous normal saline hydration. He was discharged home on the fourth day after presentation.

A follow-up brain MRI 1 month after ED presentation showed resolution of the previously reported lesion (figure 2). Subsequently, the patient received two cycles of FOLFIRI/bevacizumab but without 5-FU, until dihydropyrimidine dehydrogenase assay results were reported. Dihydropyrimidine dehydrogenase level was normal. He then received his fourth cycle of FOLFIRI/bevacizumab with a lower dose of 5-FU (1500 mg/m²) without similar symptoms. Subsequently, his restaging workup showed disease progression, so the patient's treatment regimen was changed.

DISCUSSION

5-FU is a common antineoplastic and antimetabolic agent used to treat a broad range of solid tumours, including gastrointestinal, breast, and head and neck cancers. A patient with 5-FU neurotoxicity may present with confusion, agitation, ataxia, seizures and coma. A DW-MRI brain is useful in the diagnosis of this unique encephalopathy as it shows diffusion-restricted lesions in the deep cerebral white matter and corpus callosum on T2-weighted images.^{2,3}

5-FU-induced encephalopathy is diagnosed primarily by exclusion. The commonly used clinical diagnostic criteria are (a)

Figure 2 A follow-up multisequence MRI of brain taken 1 month after the presentation to the emergency department. (A, B) The resolution of the previously shown lesion on the splenium of the corpus callosum.

development of encephalopathy during or shortly after completion of 5-FU therapy; (b) exclusion of other metabolic or physical factors that may affect the level of consciousness and (c) exclusion of drug effects by concomitant medications. Diagnosing 5-FU-induced encephalopathy is often difficult because it is uncommon, and therefore, may not be immediately recognised.

Our patient received three cycles of FOLFOX/bevacizumab chemotherapy and one cycle of FOLFIRI/bevacizumab before presenting to the ED. Leucovorin, a compound similar to folinic acid, has almost no side effects of its own. Concomitant use of leucovorin with 5-FU is essential because leucovorin increases the intracellular concentration of 5-FU in the tumour, and hence enhance the antineoplastic activities.⁴ Irinotecan binds reversibly to topoisomerase I-DNA complex, leading to termination of cellular replication. Irinotecan in combination with 5-FU and leucovorin has shown a reduction in the catabolism of 5-FU, and the combination of irinotecan with F-5-FU in FOLFIRI has shown increased risk of gastrointestinal side effects.^{5,6} Irinotecan alone is an unlikely cause of this patient's encephalopathy. The patient had only received irinotecan once when he presented to the ED; it is unclear whether the combination of irinotecan and 5-FU played a role in the pathogenesis of his encephalopathy.

Bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor, has been linked to posterior reversible leukoencephalopathy syndrome, which is characterised by headache, hypertension, confusion, visual disturbance, and seizure accompanied by subcortical vasogenic oedema predominantly in the parietal and occipital lobes, as evidenced by MRI.⁷ Most (approximately 98%) of the time, lesions are not diffusion restricted.^{8,9} Our patient lacked all the above features except for confusion; we, therefore, excluded bevacizumab toxicity as the cause of the presentation in this patient.

According to the literature, 5-FU-induced encephalopathy may develop after the first cycle or any subsequent cycle of 5-FU. This unique 5-FU side effect is uncommon (<1%) at the current standard infusion dose of 2400 mg/m² over 46 hours every 2 weeks, although approximately 6% of patients receiving a higher dose of 5-FU develop encephalopathy.¹⁰ The exact pathogenesis of 5-FU-induced encephalopathy is unclear, but two different pathways may contribute to the development of this toxicity. First, dihydropyrimidine dehydrogenase is a major enzyme inactivating 5-FU, and its deficiency may enhance accumulation of 5-FU and its toxicities. Second, the high-dose administration of 5-FU induces accumulation of catabolites such as fluoroacetate and directly inhibits the Krebs's cycle, which fosters transient hyperammonaemia due to impairment of adenosine triphosphate-dependent urea cycle.¹¹ In our patient, both dihydropyrimidine dehydrogenase and serum ammonia levels were normal, suggesting that some other factor must be involved in the pathogenesis of this unique drug toxicity. Several aggravating factors such as dehydration, renal dysfunction, constipation, and body-weight loss have been attributed to its development. Our patient had a mild renal impairment at baseline. The presence of chemotherapy-induced nausea and vomiting might have contributed to dehydration and worsened renal function in our patient.

Many patients with 5-FU-induced encephalopathy have hyperammonaemia and, when present, hyperammonaemia can provide a clinical clue towards the diagnosis of this unique drug toxicity. Signs or symptoms from hyperammonaemic encephalopathy typically appear within 72 hours after initiation of a 5-FU infusion. Reported case reports have explained 5-FU-induced hyperammonaemic encephalopathy in the absence of liver disease or another identifiable cause^{3,12-14}; further, hyperammonaemia encephalopathy with normal liver function

has been reported in patients with other conditions, such as transplant and bariatric surgery.¹⁵⁻¹⁷ Only a few reported cases of this unique encephalopathy in patients with normal serum ammonia levels have been published.^{2,18} Interestingly, several cases of 5-FU-induced encephalopathy have reported in patients who also had elevated BUN/creatinine and lactate of unclear aetiology.^{10,13,14,18} Our patient had elevated lactate, serum bilirubin, and BUN/creatinine at initial presentation to the ED, all of which trended back to baseline within 24 hours. The transient rise in bilirubin, mainly indirect, is likely secondary to irinotecan use. SN-38, an active metabolite of irinotecan, undergoes glucuronidation in the liver and competitively inhibits bilirubin glucuronidation.¹⁹

To our knowledge, this is the first reported case of 5-FU-induced encephalopathy with an isolated reversible lesion on the splenium of the corpus callosum. In our patient, DW-MRI showed an isolated diffusion-restricted lesion on the splenium of the corpus callosum at baseline that completely resolved within a month, suggesting the presence of cytotoxic oedema that can normalise with the improvement of clinical symptoms. Reversible lesions on the splenium of the corpus callosum have been associated with several disorders of diverse origins, including infection, seizure, withdrawal of seizure medication, high-altitude cerebral oedema, hypoglycaemia, electrolyte imbalance and haemolytic-uraemic syndrome.²⁰ The clinical improvement usually occurs earlier than radiological improvement in survivors. Yi *et al* and Cheung *et al* reported the cases of 5-FU-induced encephalopathy without lesions in DW-MRI, interestingly, both the cases developed the encephalopathy within 24 hours of the start of 5-FU infusion.^{13,14} Mehta *et al* reported a case of 5-FU-induced acute leukoencephalopathy with diffusion-restricted lesions in the bilateral deep white matter, cerebellar peduncles and splenium of corpus callosum 2 weeks after receiving the third cycle of 5-FU-based chemotherapy.²¹

The prognosis for 5-FU-induced encephalopathy is usually good if it is recognised early and managed properly. 5-FU-induced encephalopathy is a dose-dependent and rate-dependent toxicity. Typically, the way to manage drug toxicity is to discontinue use of the offending drug. Acute management modalities include intravenous hydration, discontinuation of the offending 5-FU (if the infusion is running) and symptom management. When the ammonia level is elevated, use of oral lactulose as a laxative is recommended to lower it. Permanent discontinuation of the 5-FU or infusion in lower dose in subsequent therapy is highly recommended. Our patient received an empirical dose of antibiotics in the ER, although no signs of infection were identified in the subsequent investigation.

In conclusion, 5-FU-induced encephalopathy is a rare but potentially fatal toxicity of 5-FU-based chemotherapy. Patients may present with confusion and profound agitation. The presence of hyperammonaemia may only be a clue in clinical diagnosis, given that a normal serum ammonia level does not preclude a diagnosis of 5-FU-induced encephalopathy. It is essential that treating oncologists, emergency physicians and others in the medical community know about and understand this potentially fatal drug toxicity to provide timely diagnosis and proper treatment to prevent irreversibility and mortality. DW-MRI can be a valuable modality for early detection of this unique encephalopathy. Further research is needed to improve our understanding of the pathogenesis of 5-FU-induced encephalopathy.

Learning points

- ▶ 5-Fluorouracil (5-FU)-induced encephalopathy may develop in the patients with normal dihydropyrimidine dehydrogenase level.
- ▶ The presence of hyperammonaemia may only be a clue in clinical diagnosis, given that a normal serum ammonia level does not preclude a diagnosis of 5-FU-induced encephalopathy.
- ▶ This is the first case of 5-FU-induced encephalopathy in our knowledge showing the diffusion-restricted lesion only on splenium of the corpus callosum in the diffusion-weighted-MRI brain.
- ▶ Management with intravenous hydration, discontinuation of the offending 5-FU (if the infusion is running) and symptomatic treatment are often enough if this unique encephalopathy is recognised in time. When the ammonia level is elevated, use of oral lactulose as a laxative is recommended to lower it.
- ▶ Emergency physicians, general practitioners and oncologists should be aware of having early diagnosis and proper treatment of this rare but life-threatening toxic effects of 5-FU-based chemotherapy.

Contributors TWR provided initial medical care to the patient and identified the case as one of significant interest, provided the initial concept, revisions and editorial review. GA formulated the body of the manuscript and provided the response to reviewers comments. MTCC provided the revisions and response to the reviewer's comments.

Competing interests None declared.

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