

A unique presentation of 5-fluorouracil (5-FU) induced cerebral encephalopathy

Shailendra S Naik, Ilavarasi Vanidassane¹, Ekta Dhamija, Atul Sharma¹

Departments of Radiodiagnosis and ¹Medical Oncology, IRCH, AIIMS, New Delhi, India

Correspondence: Dr. Atul Sharma, Department of Medical Oncology, IRCH, AIIMS, New Delhi - 110 029, India. E-mail: atul1@hotmail.com

Abstract

5-Fluorouracil (5-FU), a commonly used antimetabolite and antineoplastic agent, has been approved for the treatment of various cancers. It is associated with systemic side-effects such as gastrointestinal problems, neutropenia. 5-FU-related encephalopathy is very rarely reported. Imaging with computed tomography (CT) and magnetic resonance imaging (MRI) plays a key role in diagnosing and monitoring the changes. Since the prognosis of cerebral involvement is usually good if recognized and treated in time, the reporting radiologist and treating physician should be familiar with them. We present a rare case of 5-FU-induced encephalopathy that was diagnosed based on her clinical and MRI findings and managed successfully.

Key words: Chemotherapy; drug-induced encephalopathy; encephalopathy; 5-fluorouracil

Introduction

Colon cancer is the 4th most common malignancy among women and 3rd most common among men in India and is one of the leading cause of cancer-related mortality. Colon cancer is well known for its excellent responsiveness to chemotherapy compared with the other gastrointestinal tract cancer and chemotherapy has been given to patients with advanced colon cancer as an adjuvant or palliative treatment modality. Fluorouracil (5-FU), a pyrimidine antimetabolite has been widely used in the chemotherapy of colon cancer since its introduction in 1957. Very few cases of neurological adverse events of 5-FU have been reported till date. Among them, encephalopathy is rare and may present as disorientation, confusion, agitation, neurosensory hearing impairment, seizure, stupor, and even deep coma. We report here a patient who developed acute neurotoxicity after systemic chemotherapy with continuous infusion of 5-FU and was diagnosed and managed successfully.

Case

A 43-year-old female, known case of hypothyroidism presented with h/o bleeding per rectum and increased frequency of stools for 1 month. Colonoscopy revealed 5 cm × 7 cm ulceroproliferative growth in rectum 2 cm above the anal verge. A rectal biopsy was suggestive of adenocarcinoma. She was planned for neoadjuvant chemotherapy with FOLFOXIRI after discussion in a multidisciplinary tumor board. This regimen consisted of irinotecan 165 mg/m², oxaliplatin 85 mg/m², folinic acid 400 mg/m², and 5-FU 400 mg/m² bolus on day 1, followed by 5-FU 3200 mg/m² by continuous infusion over the next 46 hours. She was discharged with an ambulatory 5-FU pump. After 24 hours of infusion, patient presented with complaints of diarrhea, palpitations, and vomiting. She was started on IV fluids and supportive measures. On day

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3, she was agitated and developed an acute confusional state. On examination, she was disoriented and GCS was 9/15. Meningeal signs were negative and there were no focal neurologic deficits. She had urinary incontinence, pupils were reactive, and plantar extensors signs were positive. Blood pressure was normal throughout her presentation. Her initial lab investigations showed normal complete blood cell count, liver function tests, kidney function tests, electrolytes, and thyroid function. non-contrast CT head was normal [Figure 1]. Her 5-FU infusion was completed by this time. Over the next few hours, the patient's mental status progressively deteriorated to a comatose state. Subsequently performed contrast-enhanced MRI brain showed focal hypointensity in the splenium of the corpus callosum on T1, which was hyperintense on T2/FLAIR and showed restriction on diffusion-weighted image (DWI) with ADC value of 308 mm²/sec. A similar finding was found in the bilateral middle cerebellar peduncle where ADC was approximately 523 mm²/sec. Ill-defined hyperintensity at bilateral parieto-occipital white matter was also present [Figures 2 and 3]. None of these lesions show contrast enhancement. With due consideration to this detailed clinical findings and correlation. The final diagnosis of drug-induced encephalopathy was made and further 5FU-based therapy was withheld. She gradually improved with supportive measures and was discharged after a week. She was started on IROX + Bevacizumab (irinotecan 200 mg/m², oxaliplatin 65mg/m², bevacizumab 7.5 mg/kg). She tolerated her 1st cycle well without any immediate side effects. She was asymptomatic and neurological examination was normal after one month of her presentation

to an emergency. Follow-up non contrast MRI after 1 month showed persistent T2 hyperintensity at splenium and middle cerebellar peduncle but with an increase in ADC value (540 mm²/sec and 600 mm²/sec, respectively). As hyperintensity in the T2 weighted image takes a longer time for a resolution than that in DWI, findings were indicative of improvement [Figures 4 and 5]. In view of 5 FU toxicity, she was started on a regimen containing irinotecan, oxaliplatin, and bevacizumab. She tolerated the subsequent chemotherapy without any significant adverse effects. She attained partial response and underwent surgery successfully.

Discussion

5-FU is a relatively safe drug approved for the management of carcinoma colon with side effects ranging from nausea, vomiting, and diarrhea. CNS toxicity is uncommon and is limited to very few case reports.^[1-3] CNS toxicity occurs in the form of sudden onset of slurred speech, confusion, cognitive disturbances, and paranoia. These symptoms usually develop within 7 days from the beginning of the chemotherapy cycle as seen in our patient (on Day 3) and resolve on discontinuation of the drug.

Imaging plays a significant role in depicting the lesions, their location, and extent. CT may be normal or inconclusive but MRI owing to its better resolution demonstrates lesions well. DWIs and ADC maps can show these lesions due to edema within intramyelinic cleft, which is a potential extracellular



Figure 1: Axial scan NCCT Head at the level splenium of the corpus callosum is normal

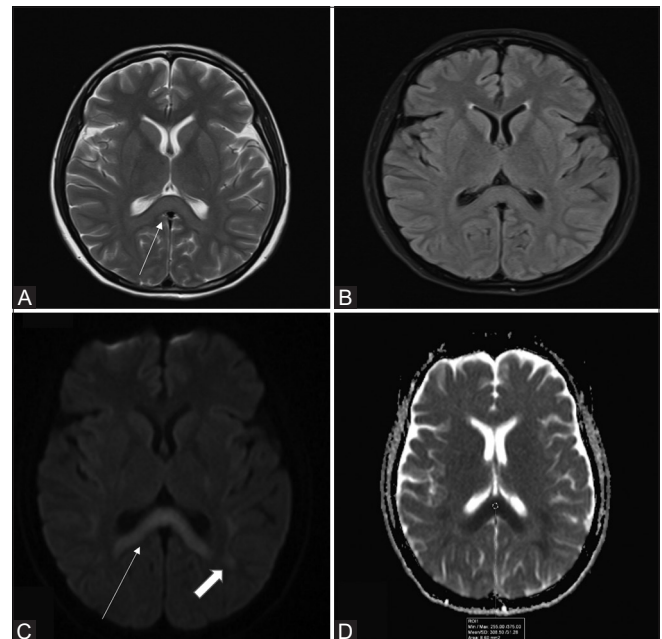


Figure 2 (A-D): Magnetic resonance imaging (Brain) axial images-showing hyperintense signals in bilateral parieto-occipital white matter (thick arrow) and splenium of corpus callosum (linear arrow) on axial T2-weighted image (A), and FLAIR (B). DWI (C) and ADCmap (D) are evident of diffusion restriction

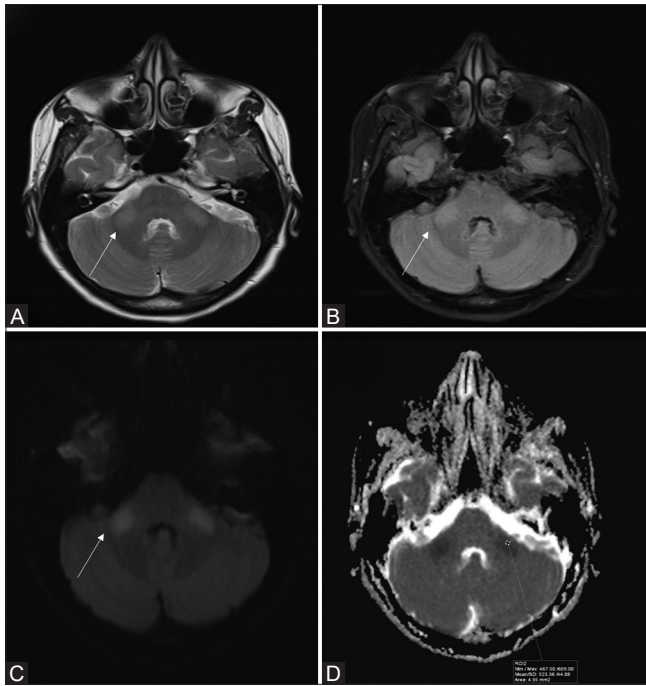


Figure 3 (A-D): Magnetic resonance imaging (Brain) axial images-showing hyperintense signals in bilateral middle cerebral peduncles (linear arrow) on axial T2-weighted image (A), and FLAIR (B). DWI (C) and ADC map (D) is evident of diffusion restriction

space and is reversible when toxicity is withdrawn. Deep white matter and corpus callosum are the reported sites of involvement.^[2,3] However, the aforementioned patient also had involvement of the middle cerebral peduncle.

The reversible lesion in the splenium of the corpus callosum and middle cerebral peduncle has a vast differential diagnosis and has been reported in a variety of neurologic and non-neurologic conditions. Such uncommon case emphasizes the importance of clinico-radiological correlation to rule out differentials like infection, demyelination, epilepsy, vascular (hypertensive encephalopathy, PRES, Preeclampsia), metabolic (hypoglycaemia, hypo/hyponatremia), axonal injury, and drugs.^[4]

Amongst drugs, cyclosporine, 5FU, and metronidazole are known to cause such imaging features in the splenium and cerebral peduncle.^[4] The disease mechanism of 5-FU encephalopathy is unclear. The toxicity of 5-FU is strongly influenced by the dosage used and the rate and duration of drug administration. Some researchers believe that accumulated fluoroacetate, which is a product of 5-FU catabolism, inhibits the Krebs cycle enzyme leading to impairment of the urea cycle and accumulation of ammonia leading to encephalopathy.

The diagnosis of 5-FU-related encephalopathy is a diagnosis of exclusion. The development of encephalopathy during or shortly after the completion of 5-FU administration and exclusion of other metabolic factors that may affect a

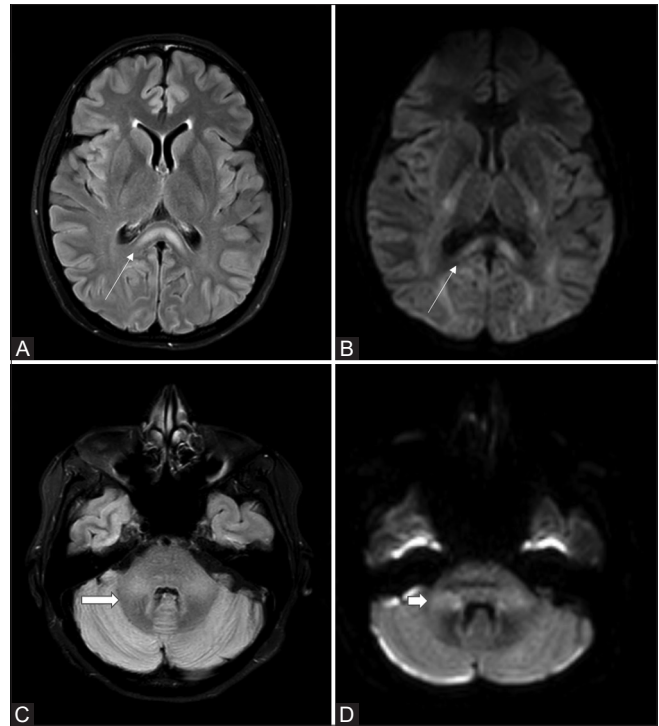


Figure 4 (A-D): Repeat magnetic resonance imaging (Brain) -showing persistent hyperintense signals in the splenium of corpus callosum (linear arrow) on axial FLAIR (A), and diffusion-weighted image (B). Similar findings at the level of MCP (thick arrow) on FLAIR (C) and diffusion-weighted image (D)

patient's consciousness and mental functioning, such as hypoglycemia, organ failure, electrolyte imbalance, sepsis, central nervous system involvement by cancer, adverse effect by concomitant medications is needed before its diagnosis. Serum dihydropyrimidine dehydrogenase (DPD) level can be assessed in patients before starting 5-FU as DPD is an important catalyst in amino acids—thiamine and uracil (i.e., ingredient of 5FU) metabolism and its deficiency leads to the accumulation of fluoropyrimidine causing neurological and GIT symptoms. In our patient, serum DPD and ammonia levels were normal. After exclusion of all common metabolic causes and based on radiology we made a final diagnosis of 5FU-induced encephalopathy. Our case highlights the rare but important complication of 5FU-containing chemotherapy and also describes the unique finding in MRI of our patient. To our knowledge, this is a first reported case where curative surgical resection of the tumour was done after irinotecan-based regimen following an episode of 5FU-induced encephalopathy in the neoadjuvant setting.

Conclusions

Encephalopathy due to 5FU is very rare. Early recognition and withdrawal of the culprit drug lead to clinical improvement. Imaging plays a vital role in the demonstration of lesions in neuroparenchyma. Awareness of this entity

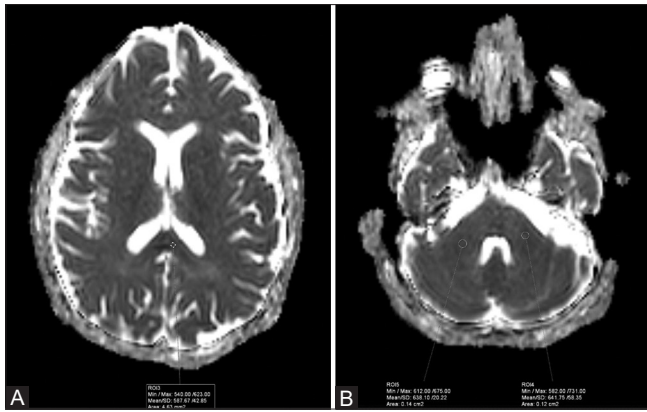


Figure 5 (A and B): ADC maps at splenium (A) and MCP (B) showing persistent restriction with increased values

amongst reporting radiologist and clinicians along with clinico-radiological correlation is essential for the successful management of these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and

other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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