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CASE REPORT

5-Fluorouracil-induced leukoencephalopathy in a patient with gastric adenocarcinoma: A case report

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A B S T R A C T

Acute encephalopathy is one of the rare neurotoxic side effects of 5-Fluorouracil with only a few case studies published in the literature. Clinical manifestation of 5-FU-induced leukoencephalopathy is characterized by disorientation, confusion, seizure, and unconsciousness. We present a case of acute leukoencephalopathy in a 32 years old female, with locally advanced poorly differentiated gastric adenocarcinoma undergoing treatment using the 5-fluorouracil-leucovorin-oxaliplatin-docetaxel (FLOT) regimen. The patient was reported with acute delirium, aphasia, acute confusional state, low Glasgow Coma Score (CGS), and irritability within 24 hours of her first FLOT cycle, which was administered to her for the treatment of gastric adenocarcinoma. A diffusion-weighted (DW)-MRI brain scan showed a bilateral symmetrical diffusion-restricted lesion in the white matter. A diagnosis of leukoencephalopathy was made based on clinical and radiological workup. 5-Fluorouracil was stopped and commenced on methylprednisolone and had a dramatic recovery. The onboard oncologists must be aware of this unusual toxicity of 5-Fluorouracil to initiate prompt treatment as this is largely a reversible complication.

Keywords: *Fluorouracil; Leukoencephalopathies; Adenocarcinoma; Chemotherapy*

Introduction

Acute encephalopathy is one of the rare neurotoxic side effects of 5-Fluorouracil (5-FU) with only a few case studies published in the literature. Lesions of the brain identified on an MRI after 5-FU induction in patients are often associated with 5-FU-induced encephalopathy. The characteristic findings are dispersed and include high signal intensity in the deep cerebral white matter and corpus callosum.[1] Although Fluorouracil (5-FU) has been approved for the treatment of a variety of cancers, its use has also been reported to potentially cause a wide array of cardiac toxicity manifesting as cardiomyopathy, ventricular arrhythmias, and sudden cardiac death.[2] Leukoencephalopathy itself is one of the rarest side effects linked to 5-FU chemotherapy. Clinical manifestation of 5-FU-induced leukoencephalopathy is characterized by disorientation, confusion, seizure, and unconsciousness.[3] We present a case of acute leukoencephalopathy in a patient with locally advanced poorly differentiated gastric adenocarcinoma undergoing treatment using the 5-fluorouracil-leucovorin-oxaliplatin-docetaxel (FLOT) regimen. Ethical Approval Statement: Ethical approval was obtained from the Institutional Review Board (IRB) of Shaukat Khanum Memorial Cancer Hospital & Research Center in compliance with the ICH-GCP guidelines. Approval no. EX-10-05-24-02.

Case report

A 32-year-old, married, female was presented to the outpatient department (OPD) of Shaukat Khanum Memorial Cancer Hospital Research Centre (SKMCH&RC) Peshawar. The patient presented with complaints of abdominal pain, indigestion, weight loss, and vomiting for 8 months. Upon examination, the abdomen was soft and nontender. An endoscopy was performed and was followed by a biopsy, CT scan, and PET-CT scan. After detailed imaging and biopsy, a diagnosis of T3N1M0 locally advanced poorly differentiated gastric adenocarcinoma was made. A staging laparoscopy was performed which showed a tumor in the stomach involving the fundus, sparing the gastroesophageal junction and pylorus. There was no omentoperitoneal disease or ascites seen. The fluid cytology findings were negative. Her case was discussed in the weekly meeting of the multidisciplinary team of the institute, where she was planned for perioperative chemotherapy followed by surgery. She was started on a 5-fluorouracil-leucovorin-oxaliplatin-docetaxel (FLOT) regimen as per institutional guidelines. The FLOT chemotherapy regimen doses were docetaxel (60 mg/m^2), oxaliplatin (85 mg/m^2), leucovorin (200 mg/m^2), and 5-fluorouracil (2,600 mg/m^2) as a 24-hour infusion.

The patient after receiving only one cycle of FLOT was presented to the emergency department (ED) the following day. The patient was reported with acute delirium low GCS, aphasia, acute confusional state, and irritability. She was not capable of following simple commands and was unable to respond to any question. Her blood pressure was 90/60 mm Hg. The metabolic profile was unremarkable. The patient was shifted to the Intensive Care Unit (ICU) due to worsening of GCS where her blinking dropped, and she was not responding to any verbal commands. She underwent a CT brain which was unremarkable. Her lumbar puncture was performed. On cerebrospinal fluid analysis, there were remarkably elevated levels of proteins 315 mg/dL (normal range 20-40 mg/dL) and glucose was within the normal range. Negative staining with India INK Stain for cryptococcus neoformans ruled out Cryptococcus meningitis. A diffusion-weighted (DW)-MRI brain scan showed a bilateral symmetrical diffusion-restricted lesion in the white matter involving corona radiata and centrum semiovale as shown in Figures 1 and 2.

A diagnosis of leukoencephalopathy was made based on clinical and radiological suspicion. 5-FU was stopped and she was commenced on pulse methylprednisolone 1 gm for 3 days. The patient completed a 3-day course of methylprednisolone and had a dramatic recovery. Her GCS score improved from 3/15 to 15/15. The patient was now well mobilized with no weakness, headache, or vomiting. Her remaining course of chemotherapy was completed with a slow and desensitization approach.

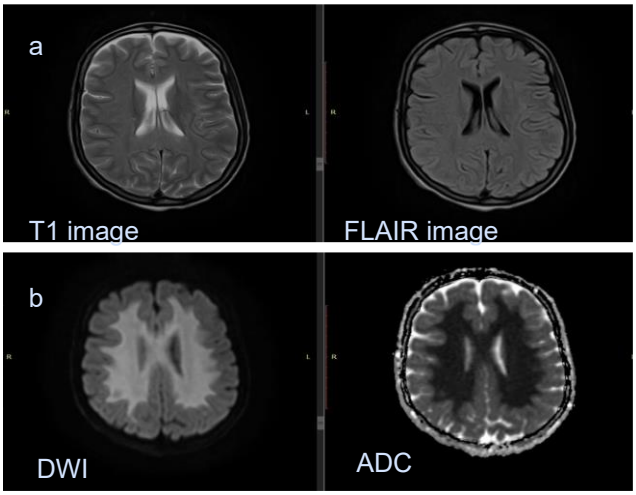

Figure 1: (a) Subcortical U-fibers are more prominent than expected on a standard T2 MRI and fluid-attenuated inversion recovery (FLAIR) MRI images. (b) Diffusion-weighted image (DWI) shows diffusely increased signal in white matter confirmed as a true restriction on apparent diffusion coefficient (ADC) map.

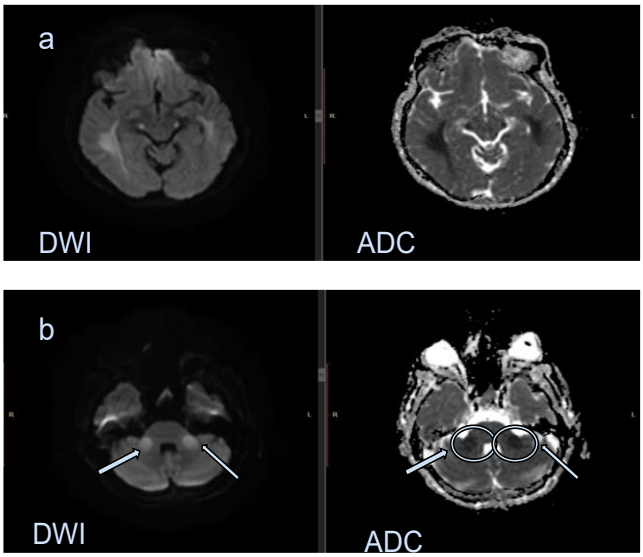

Figure 2: (a) Diffusion restriction in the white matter tract on a DWI and ADC MRI images.
(b) Diffusion-weighted image shows extension into middle cerebellar peduncles, also visible on the ADC image of the MRI.

The patient completed cycles of FLOT with reduced doses and had no acute reactions. She had also undergone total gastrectomy with curative intent. She is now being scheduled for the remaining FLOT chemotherapy. This case highlights the need for awareness of this unusual toxicity of 5 FU to initiate prompt treatment as this is a life-threatening complication.[4]

Discussion

Leukoencephalopathy is one of the rarest side effects linked to 5-FU chemotherapy. Patients presenting with disorientation, confusion, seizure, and unconsciousness post-5-FU chemotherapy induction should be suspected for 5-FU induced leukoencephalopathy as its early detection and drug discontinuation can reverse the clinical symptoms.[3]

To our understanding, the definite pathogenesis of 5–FU–induced leukoencephalopathy is not known. However, previously published studies point toward two mechanisms that might have contributed to the emergence of this toxicity. One is the deficiency of the enzyme dihydropyridine dehydrogenase, which functions in deactivating 5-FU, leading to toxic accumulation of 5-FU. The other is the transient elevation of ammonia levels in the blood due to dysfunction of the adenosine triphosphate-dependent urea cycle on account of the Krebs cycle being directly inhibited by the accumulation of 5-FU catabolite fluoroacetate due to its high dose administration. Given that both the dihydropyrimidine dehydrogenase and serum ammonia levels of our patient were within normal range, the possibility for the above-mentioned pathogenesis seems inconsequential.[1,4] The factor involved in the pathogenesis of this rare toxicity of 5-FU needs to be investigated further.

Literature suggests that the chemotherapeutic agent, 5-FU, is responsible for neurotoxicity in less than 5% of cases. A recent case, described by Hamid Ziani et al. in 2024, involved a patient with comparable symptoms after 5-FU-based chemotherapy for gastric adenocarcinoma, and whose MRI scan revealed signs suggestive of toxic leukoencephalopathy, further illustrating the consistency of this potential side effect across similar studies.[5] Since 5-FU-induced leukoencephalopathy is a reversible complication, it usually has a good prognosis if diagnosed promptly. In a study by Manikandan et al. in 2023 it was observed that 5-FU-induced encephalopathy holds a good prognosis if diagnosed and treated promptly, and irreversible damage and mortality in patients can thus be prevented [3]. Low-dose infusion in subsequent therapy or complete discontinuation of 5-FU is generally recommended [6]. Having stopped the 5-FU, our patient received pulse methylprednisolone 1 gm for 3 days as an acute management modality and made a drastic recovery. The beneficial effect of steroids on the outcome of various brain disorders featuring edema has been observed.[7,8] Hence, a positive impact of steroids based on this underlying pathophysiological process is likely responsible for the remarkable recovery. The remaining chemotherapy course was completed with reduced doses of 5-FU with no consequent acute reaction.

Conclusion

In conclusion, acute leukoencephalopathy is a rare, yet critical outcome of 5 FU-based chemotherapy. A definite diagnosis is made on DW MRI suggesting a bilateral symmetrical diffusion-restricted lesion in the white matter, making it a great diagnostic modality. Since the addition of steroids resulted in a swift recovery of the patient from the neurological symptoms, it implies that steroids may provide a therapeutic benefit in the setting of

5 FU-induced leukoencephalopathy. The onboard oncologists must be aware of this unusual toxicity of 5-FU to initiate prompt treatment as this is largely a reversible complication.

Patient Consent: Informed consent was taken from the patient to share her history and scans and for the publication of this case report.

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