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Acute 5-Fluorouracil-Induced Leukoencephalopathy During Neoadjuvant Flot Chemotherapy In Gastric Cancer: A Case Report

Naveenraj Viswanathan, Flencinecia Basil Raj, Shalini Prabhakar, Ram Kumar Mummoorthy, Vijayakumar Arumugam

(Clinical Pharmacist, Department Of Hematology And Oncology, Kovai Medical Center And Hospital, Coimbatore – 641014, India).
(Consultant Medical Oncologist, Department Of Medical Oncology, Kovai Medical Center And Hospital, Coimbatore – 641014, India).
(Head – Pharmacy Services, Kovai Medical Center And Hospital, Coimbatore – 641014, India).

Abstract:
5-Fluorouracil (5-FU)-induced leukoencephalopathy represents an infrequent yet potentially reversible neurotoxic consequence associated with chemotherapy regimens when diagnosed earlier. This study presents a case involving a 51-year-old male diagnosed with gastric adenocarcinoma (cT3N2M0) who was subjected to neoadjuvant FLOT chemotherapy and subsequently experienced acute neurological manifestations during the second cycle, characterized by confusion, dysarthria, and agitation. A magnetic resonance imaging (MRI) of the brain demonstrated symmetrical alterations in white matter, aligning with the diagnosis of toxic leukoencephalopathy. Notably, despite possessing a wild-type dihydropyrimidine dehydrogenase (DPYD) gene, the patient manifested severe neurotoxic effects. The infusion of 5-FU was discontinued, and the patient received a treatment regimen comprising thiamine, methylcobalamin, levetiracetam, and corticosteroids, culminating in a complete recovery of neurological function. This case underscores the imperative for prompt recognition and intervention regarding 5-FU-induced neurotoxicity, as timely management can mitigate the risk of enduring complications. Furthermore, it accentuates the observation that neurotoxicity may arise in patients devoid of DPYD mutations, thereby necessitating vigilant neurological surveillance for all individuals undergoing 5-FU-based therapeutic protocols. Additional research is warranted to elucidate supplementary risk factors and to enhance preventive methodologies.

Keywords: *5-Fluorouracil (5-FU), Leukoencephalopathy, Neurotoxicity, Gastric adenocarcinoma, Chemotherapy-induced toxicity*

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I. Introduction

5-Fluorouracil (5-FU) represents a commonly employed chemotherapeutic agent, predominantly utilized in the management of solid tumours such as colorectal, breast, and gastrointestinal malignancies. It functions as an antimetabolite, interfering with the synthesis of DNA and RNA, ultimately culminating in apoptosis in rapidly proliferating neoplastic cells. Although 5-FU is typically well-tolerated, its adverse effects may extend from mild gastrointestinal disturbances to severe complications, including neurotoxicity[1]. Among the neurological sequelae, 5-FU-induced leukoencephalopathy constitutes a rare yet potentially life-threatening side effect that primarily impacts the white matter of the brain[2].

Leukoencephalopathy is characterized by demyelination of cerebral white matter, resulting in neurological manifestations such as confusion, ataxia, dysarthria, seizures, and, in extreme cases, coma[3]. The precise pathophysiological mechanism remains incompletely elucidated, but it is hypothesized to involve disruptions in pyrimidine metabolism, mitochondrial dysfunction, and direct cytotoxicity to oligodendrocytes[4]. Diagnosis primarily relies on magnetic resonance imaging (MRI) findings, which typically reveal bilateral, symmetric hyperintensities in the periventricular and subcortical white matter[5]. Timely cessation of 5-FU and the administration of uridine triacetate, an antidote for fluoropyrimidine-induced toxicity, are imperative for facilitating recovery. This case report discusses the presentation, diagnosis, and management of a patient with 5-FU-induced leukoencephalopathy, highlighting the importance of early recognition and intervention to prevent long-term neurological sequelae.

II. Case Description

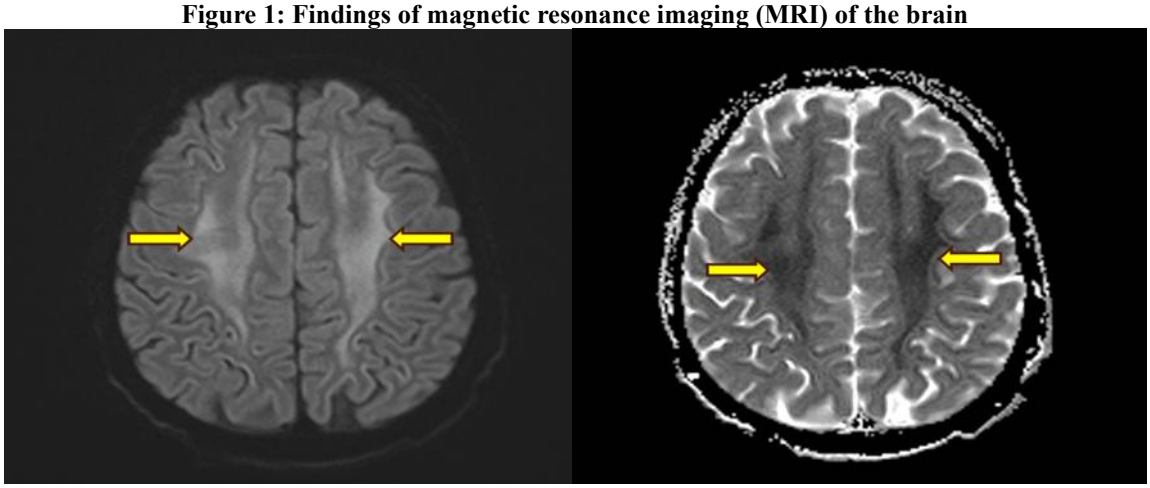
A 51-year-old male patient was subjected to a comprehensive evaluation for the persistent manifestations of abdominal pain and emesis over ten days. On the day of admission, laboratory evaluations, which encompassed a complete blood count (CBC), serum electrolyte levels, renal function assays, and inflammatory biomarkers, yielded results that were within normal ranges. An upper gastrointestinal endoscopy elucidated the presence of a prepyloric neoplasm that extended proximally to the incisura and distally to the junction between the first and second portions of the duodenum. Histopathological analysis corroborated a diagnosis of poorly differentiated adenocarcinoma of the stomach. Subsequent staging investigations classified the malignancy as cT3N2M0 gastric carcinoma. Genetic testing confirmed that the patient possessed a wild-type DPYD gene, indicative of a typical metabolic response to fluoropyrimidines. In light of the tumor's locally advanced classification, a neoadjuvant FLOT regimen was administered, which comprised 5-Fluorouracil (5-FU) at a dosage of 2,400 mg/m² delivered via intravenous infusion for 46 hours, leucovorin at 200 mg/m², oxaliplatin at 85 mg/m², and docetaxel at 50 mg/m², all planned in cycles of three weeks. The initiation of the first cycle commenced at 80% of the standard dosageto balance treatment efficacy with patient safety, with subsequent cycles reverting to the full 100% dosage from the second cycle onward.

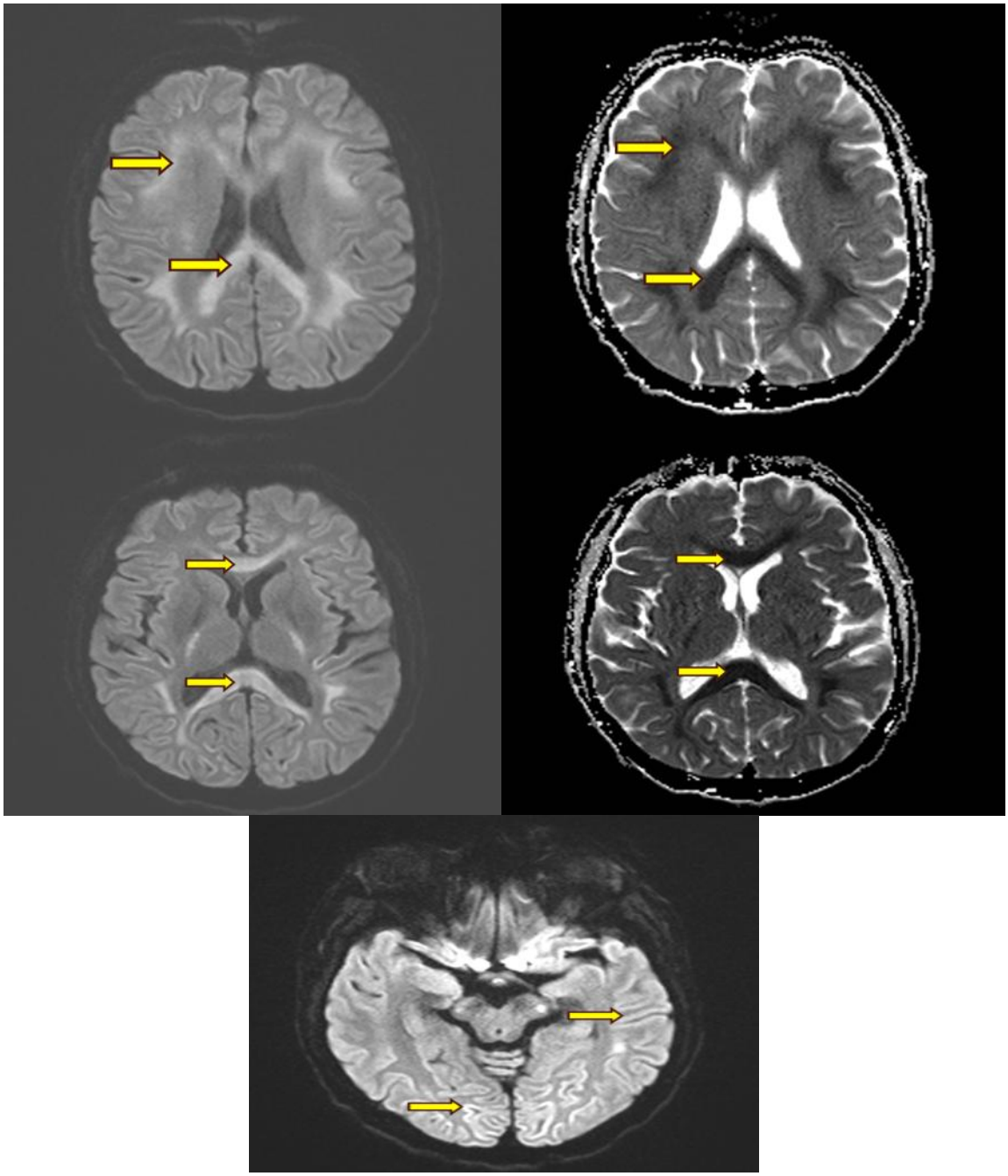
During the second cycle of chemotherapy, while undergoing continuous infusion of 5-FU, the patient presented to the emergency department exhibiting severe emesis, rigors, palpitations, and hypotension (80/40 mmHg). The infusion of 5-FU was terminated at 40 hours, deviating from the planned 46 hours due to clinical deterioration. The patient was promptly commenced on noradrenaline, intravenous fluids, and various supportive care measures. Given the clinical presentation, sepsis was considered an initial differential diagnosis, necessitating the procurement of blood and urine cultures alongside broad-spectrum antibiotic therapy. The central chemo-port was flushed with gentamicin to avert catheter-associated bloodstream infections. A cardiac assessment, inclusive of echocardiography (ECHO), revealed an ejection fraction of 60%, effectively ruling out the presence of acute cardiac dysfunction.

The CBC results demonstrated post-chemotherapy leukopenia with a count of 3,000 cells/mm³, hemoglobin levels at 10.7 g/dL, and a platelet count of 181,000/µL, all of which fell within clinically acceptable parameters. Serum electrolyte levels were unremarkable (sodium at 137 mEq/L and potassium at 4.5 mEq/L). However, renal function tests displayed abnormalities, characterized by elevated serum creatinine levels at 1.6 mg/dL and blood urea nitrogen at 46 mg/dL. C-reactive protein (CRP) levels were recorded at <6 mg/dL, signifying an absence of substantial systemic inflammatory response. Urinary microscopy yielded inconclusive results. Following termination of chemotherapy, the patient received PEG-G-CSF support.

On the third day of the second cycle of chemotherapy, the patient exhibited neurological disturbances, including confusion, agitation, dysarthria, and intermittent episodes of staring lasting between 10 to 20 seconds, suggestive of absence seizures. A neurological examination revealed preserved muscle tone and the presence of aphasia. Brain MRI findings (Figure 1) illustrated confluent, symmetrical hyperintensities within the white matter of the bilateral cerebral hemispheres, as well as in the corona radiata, corpus callosum, internal capsules, and both the cerebral and middle cerebellar peduncles, consistent with the diagnosis of acute toxic or drug-induced leukoencephalopathy.

Figure 1: Findings of magnetic resonance imaging (MRI) of the brain





MRI Brain showing confluent, symmetrical restricted diffusion in the bilateral supratentorial white matter, corpus callosum, corona radiata, and internal capsules (bright on DWI, dark on ADC), consistent with acute leukoencephalopathy. Gyriform high signal on DWI along the bilateral cerebral cortex suggests cortical involvement, likely due to 5-FU neurotoxicity

Additional diagnostic procedures included cerebrospinal fluid (CSF) analysis, which yielded normal results devoid of atypical cells in cytological evaluation. Serum ammonia levels were at normal range (58.6 µg/dL), thereby ruling out the potential for significant hyperammonemic encephalopathy. Blood and urine cultures remained sterile, effectively excluding an infectious etiology. Based on MRI findings and the clinical presentation, a diagnosis of 5-FU-induced leukoencephalopathy was established. The patient was subsequently treated with intravenous thiamine at a dosage of 200 mg/day, methylcobalamin at 1,000 mcg/day, levetiracetam at an initial dose of 1 g followed by 500 mg three times daily, and dexamethasone at 8 mg/day for five days. Gradual weaning off of noradrenaline was conducted, and the patient exhibited significant neurological recovery within one week. He was ultimately discharged in a stable condition, free from any residual neurological deficits.

III. Discussion

5-Fluorouracil (5-FU) is a widely used chemotherapeutic agent for gastrointestinal malignancies, including gastric cancer. While its common toxicities include myelosuppression, mucositis, and gastrointestinal disturbances, central neurotoxicity is a rare but potentially life-threatening complication. This case highlights 5-FU-induced leukoencephalopathy, a recognized yet underreported adverse effect. Neurotoxicity from 5-FU can present as confusion, ataxia, seizures, dysarthria, and in severe cases, coma. Symptoms typically arise within hours to days of drug administration. This case exhibited progressive confusion, agitation, and aphasia, aligning with previous reports of 5-FU neurotoxicity[5]. Magnetic resonance imaging (MRI) is the diagnostic modality of choice, revealing symmetrical T2/FLAIR hyperintensities in the periventricular white matter, corpus callosum, and internal capsules. Restricted diffusion on DWI suggests cytotoxic edema, consistent with toxic leukoencephalopathy[6]. The MRI findings in this case align with the classical radiologic features of 5-FU-induced leukoencephalopathy.

The exact mechanism underlying 5-FU-induced leukoencephalopathy remains unclear. Several proposed mechanisms include metabolic disruption, mitochondrial dysfunction, and direct white matter toxicity. Fluoropyrimidine metabolites interfere with the Krebs cycle, leading to energy depletion and neural dysfunction[4]. Additionally, 5-FU has been shown to impair astrocyte function and disrupt the blood-brain barrier, resulting in widespread white matter damage[7]. Thiamine deficiency has also been implicated in 5-FU neurotoxicity, as the drug interferes with thiamine-dependent metabolic pathways. This may lead to a clinical presentation mimicking Wernicke's encephalopathy[8]. In the present case, thiamine supplementation contributed to neurological recovery, supporting this hypothesis.

Electrolyte imbalances, fluctuations in blood glucose levels, acidosis, hypoxaemia, and organ failures—including renal and hepatic dysfunction—are all recognized causes of acute encephalopathy. In this case, however, normal electrolyte and serum ammonia levels suggest that these common factors are not responsible for the observed neurological symptoms[2]. Notably, our patient experienced mild renal impairment following the first cycle of chemotherapy. This renal dysfunction may have contributed to the development of this unique drug-induced toxicity.

The mainstay of treatment for 5-FU-induced leukoencephalopathy is immediate cessation of the drug, supportive care, and symptomatic management. Thiamine and cobalamin supplementation have been reported to aid in recovery by mitigating metabolic toxicity[9]. In this case, dexamethasone and levetiracetam were also administered, addressing potential neuroinflammation and seizure activity, respectively.Haemodialysis has been suggested for severe cases, especially in patients with renal impairment, as it can expedite the clearance of toxic 5-FU metabolites[10,11]. However, given the patient's spontaneous recovery, invasive measures were unnecessary. Also,the antidote - uridine triacetate not prescribed in this case, since in the Indian context, there is limited publicly available information regarding the availability and use of uridine triacetate for drug toxicity.

Dihydropyrimidine dehydrogenase (DPD) is the primary enzyme responsible for 5-FU catabolism. DPD deficiency leads to severe toxicity, but neurotoxicity can occur even in patients with normal DPD function[12]. This case emphasizes the need for further genetic and metabolic screening to identify patients at risk for neurotoxic events and underscores the importance of early recognition and management of 5-FU-induced leukoencephalopathy. Neurotoxicity remains an unpredictable yet serious adverse event, necessitating heightened clinical awareness. MRI plays a crucial role in diagnosis, and prompt discontinuation of 5-FU, along with supportive care, can lead to favourable outcomes. Further research is required to establish preventive strategies and optimize therapeutic approaches for this rare but serious complication.

IV. Conclusion

This case illustrates 5-FU-induced leukoencephalopathy as an uncommon yet reversible adverse effect associated with chemotherapy when diagnosed earlier. A patient diagnosed with gastric adenocarcinoma (cT3N2M0) who was undergoing neoadjuvant FLOT experienced acute neurotoxicity during the second treatment cycle, showcasing symptoms such as confusion, dysarthria, and agitation. A brain MRI corroborated the diagnosis of toxic leukoencephalopathy, which necessitated the immediate cessation of 5-FU and the initiation of supportive therapeutic measures. Timely intervention involving thiamine, methylcobalamin, levetiracetam, and corticosteroids resulted in a complete neurological recovery. This case underscores the need for vigilant monitoring for neurotoxicity in 5-FU-treated patients.

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