

5-Fluorouracil-Induced Neurotoxicity Presenting as Acute Toxic Leukoencephalopathy in a Patient with Metastatic Carcinoma Rectum: A Case Report

Dr. Gurjeet Singh Chowdhary^{1*}, Dr. Rachna Gulati², Dr. Manish Singh Ahuja³, Dr. Shalini Chowdhary⁴, Dr. Neena Katoch⁵

¹MBBS; MD (Medicine), Consultant, Department of Medical Oncology, Indus Superspeciality Hospital (ISSH), Phase 1, Mohali, Punjab

Email: gschowafmc@yahoo.com

Contact: 9167 4062 47

ORCID ID: 0000-0002-2269-3579

²MBBS, DNB (Path), Associate Professor, Department of Pathology, SGT Medical College and Hospital, Gurgaon

Email: rachnagulati22@gmail.com

³MBBS, MS (Anatomy), Professor, Department of Anatomy, SGT Medical College, Gurgaon

Email: msahujaone@gmail.com

ORCID ID: 0000-0001-8404-8420

⁴MBBS, MD (Medicine), Physician, MD, ECHS Polyclinic, Command Hospital (WC), Chandimandir-134107

Email: shalinichow0123@gmail.com

⁵Associate Professor, Department of Pharmacology, Geetanjali Medical College and Hospital, Udaipur

Email: drneenakatoch@gmail.com

*Corresponding Author: Dr. Gurjeet Singh Chowdhary, 45-A, Sector 10-A Chandigarh, Pin code: 160011

Email: gschowafmc@yahoo.com

Contact: 9167 4062 47

ORCID ID: 0000-0002-2269-3579

ABSTRACT

Fluorouracil (5-FU), despite common use in management of colorectal cancer, shows a narrow therapeutic range, with neurological toxicity. A 75-year-old man with metastatic rectal cancer developed 10–12 episodes of persistent vomiting, followed by left-sided hemiparesis and dysarthria, two days after his third FOLFIRI cycle. Initial assessment and non-contrast CT suggested an acute ischemic stroke in the right middle cerebral artery territory. However, MRI subsequently demonstrated bilateral supratentorial hyperintensities with restricted diffusion, indicating acute toxic leukoencephalopathy related to chemotherapy. DPYD genotyping revealed a wild-type status, with no detectable dihydropyrimidine dehydrogenase deficiency. The patient was treated conservatively with intravenous fluids and supportive measures, resulting in significant neurological recovery and mRS score of 1 at discharge. This case demonstrates that 5-FU-associated neurotoxicity may occur despite the absence of DPYD mutations and highlights the potential importance of combining pharmacogenomic testing with phenotypic DPD assessment to improve fluoropyrimidine treatment safety.

Keywords: 5-Fluorouracil; 5-FU neurotoxicity; DPD deficiency; DPYD gene; toxic leukoencephalopathy; pharmacogenomics; precision oncology; FOLFIRI

How to cite this article: Gurjeet Singh Chowdhary^{1*} Dr. Rachna Gulati² Dr. Manish Singh Ahuja³ Dr. Shalini Chowdhary⁴ Dr. Neena Katoch⁵. 5-Fluorouracil-Induced Neurotoxicity Presenting as Acute Toxic Leukoencephalopathy in a Patient with Metastatic Carcinoma Rectum: A Case Report. *Int J Drug Deliv Technol.* 2026;16(86s):1035-1039. DOI: 10.25258/ijddt.16.86s.101.

Type of article: **Case report**

Running title: 5-Fluorouracil neurotoxicity in CA Rectum

Total number of pages: 5

Total number of photographs: Nil

Word counts for abstract: 135

Word counts for the text: 1700

Source(s) of support: None

Presentation at a meeting: None

Conflicting Interest: None

INTRODUCTION

Colorectal cancer, with 9.9% new cases and 9.4% mortality, holds a significant healthcare burden in the oncology department.¹The management remains restricted to surgery and the use of chemotherapy, with fluoropyrimidines forming the cornerstone of systemic treatment.²

5-Fluorouracil (5-FU) is one such fluoropyrimidine analogue, is used in the management of gastrointestinal malignancies, in regimes such as FOLFIRI (5-FU, leucovorin, irinotecan) and FOLFOX (5-FU, leucovorin, oxaliplatin).³ As a chemotherapy drug hematological toxicity and mucositis remain common side effects, while 0.2% to 5% exhibit neurotoxicity as a complication serious enough - characterized by confusion, psychosis, seizures, and coma in severe cases.⁴⁻⁷

The investigation for 5FU mediated neurotoxicity requires magnetic resonance imaging (MRI) testing but the findings of hyperintensity in the white matter may mimic stroke. So, along with it, genetic testing becomes important as the dihydropyrimidine dehydrogenase enzyme, encoded by the DPYD gene deficiency mainly leads to overaccumulation of the drug and toxicity;^{4,8} nonetheless, cases without genetic mutations, also exist.**Error! Bookmark not defined.****Error! Bookmark not defined.****Error! Bookmark not defined.**

Here, we report a case of 5-FU-induced toxic leukoencephalopathy following FOLFIRI chemotherapy. The rarity of the case allows for spreading awareness to the treating oncophysician and oncosurgeon for better management of the patient.

CASE HISTORY

A 75-year-old male, with a background history of type 2 diabetes mellitus (T2DM), hypertension (HTN), and a prior chronic infarct in the left parieto-occipital lobe (fully recovered), was under follow-up. He had initially presented with altered bowel habits and was diagnosed with carcinoma rectum on

colonoscopy, which revealed an ulcerated friable growth involving more than 30% of the circumferential surface, 8–10 cm from the anal verge. Rectal biopsy confirmed well-differentiated adenocarcinoma.

He completed neoadjuvant concurrent chemoradiotherapy (NACCRT; 50.4 Gy in 28 fractions). Pre-operative imaging (CT abdomen and pelvis) demonstrated an eccentric soft tissue density lesion in the anterior and left lateral wall of the rectum; MRI showed an anorectal mass lesion extending beyond the visceral peritoneum. Subsequent WB-PET CT noted FDG-avid asymmetric thickening in the lower rectum with mesorectal extension and post-treatment inflammatory changes. He underwent laparoscopy converted to open abdominoperineal resection (APR). Histopathology of the APR specimen showed moderately differentiated adenocarcinoma (mucin secreting), grade 2, with circumferential resection margins involved by invasive carcinoma.

Post-operatively, he received adjuvant CAPOX chemotherapy (5 cycles, tolerated well), followed by 3 cycles of capecitabine monotherapy. Video colonoscopy was normal.

Subsequently, CT scan of the thorax, abdomen, and pelvis revealed a peripherally enhancing lesion in the right pre-sacral region at the S5 level with subtle sacral bone erosion, raising suspicion for disease recurrence. Serum CEA was elevated at 14.21 ng/ml. CT-guided biopsy from the right sacral region yielded scanty viable tissue; repeat biopsy was performed. WB-PET CT confirmed a metabolically active soft tissue lesion at the pre-sacral operative site causing erosion of S4–S5 vertebrae, consistent with disease recurrence, alongside bilateral lung nodules suggestive of metastasis. USG abdomen showed hepatomegaly with grade 2 fatty change. 2D

echocardiography revealed LVEF of 60% with no regional wall motion abnormalities.

A chemoport was inserted into the right internal jugular vein, and second-line chemotherapy was initiated per the FOLFIRI protocol: “Irinotecan 180 mg/m² IV over 120 minutes, Leucovorin 200 mg/m² IV over 120 minutes, and 5-FU 400 mg/m² IV bolus, all on Day 1, followed by 5-FU 2400 mg/m² as a continuous IV infusion over 46 hours — planned for 6 cycles at 2-week intervals”. Pre-medication included Injection Atropine 0.3 mg slow IV, Injection Dexamethasone 8 mg, Injection Ranitidine 50 mg, and Injection Ondansetron 8 mg.

The 1st cycle was administered and was well tolerated. For the 2nd cycle, the patient presented with forgetfulness and cerebellar symptoms and was found to have leucopenia (TLC 3010/cumm), for which Injection peg-GCSF 6 mg S/C was administered stat. He received the 2nd cycle of FOLFIRI, which was tolerated; however, he developed acute urinary retention during the hospital stay, necessitating Foley catheterisation, and was referred for further urological evaluation.

He subsequently presented for his 3rd cycle of FOLFIRI and received the chemotherapy uneventfully. Approximately 48 hours after completion of the 3rd cycle, he developed 10–12 episodes of intractable vomiting followed by sudden-onset left-sided hemiparesis and dysarthria. On neurological examination, higher mental functions (HMF) were intact; power was 3/5 in the left upper and lower limbs; right upper motor neuron (UMN)-type facial palsy and slurred speech were present; deep tendon reflexes were 2+ bilaterally; plantar response was extensor on the right. NIHSS score was initially 18, rapidly improving to 2 on assessment. Vital signs were stable throughout.

The investigations done are given in Table 1.

Table 1: Investigations performed on patient

Investigation	Findings
NCCT Head	Small evolving right MCA infarct (ASPECTS 8/10) Chronic left parieto-occipital infarct Generalized cerebral volume loss No large-vessel hyperdensity sign
CT angiography: brain and neck vessels	Bilateral carotid atherosclerotic changes Nearly luminal narrowing at left

Investigation	Findings
	CCA bifurcation due to mixed-density calcific plaques No large-vessel occlusion Bilateral ACA, MCA and PCA normal in course and calibre
2D Echocardiography	LVEF 60% No regional wall-motion abnormalities No identifiable cardioembolic source
MRI brain – T2/FLAIR	Bilateral supratentorial hyperintensities with restricted diffusion Findings suggestive of acute toxic leukoencephalopathy Likely chemotherapy-induced
DPYD gene mutation analysis – PCR/sequencing	Wild-type genotype No c.2856>T, c.1905+1G>A or c.1679T>A variants No evidence of DPD deficiency on standard pharmacogenomic panel

Management and Outcome

On initial presentation, the clinical picture was managed as an acute ischaemic stroke (right MCA territory), and the patient received symptomatic treatment. Following the MRI findings suggestive of acute toxic leukoencephalopathy, 5-FU-induced neurotoxicity was strongly considered and further FOLFIRI chemotherapy was suspended. The patient was managed conservatively with intravenous fluids, neuroprotective measures, and close neurological monitoring. He demonstrated gradual and significant clinical improvement and was discharged from MDTC with a residual neurological deficit of mRS grade 1 (minor symptoms; no significant disability). Further administration of FOLFIRI was deferred pending multidisciplinary oncology review and the DPD gene analysis report, with advice to review at the Medical Oncology OPD with the 5-FU toxicity DPD gene analysis result.

DISCUSSION

This case adds to the limited number of reported instances of 5-FU-induced neurotoxicity, an uncommon but serious adverse effect of fluoropyrimidine-based chemotherapy. The underlying mechanism is thought to involve direct neurotoxicity from fluorinated metabolites—particularly fluorocitrate and fluoroacetate—which inhibit tricarboxylic acid (TCA) cycle enzymes, disrupting neuronal energy metabolism and causing diffuse white matter injury. On MRI (T2/FLAIR), this

manifests as bilateral, often symmetric, supratentorial white matter hyperintensities with restricted diffusion, a pattern consistent with toxic leukoencephalopathy.⁸

The present case was an elderly 75-year-old male with comorbidities in the form of hypertension and diabetes mellitus, with a prior infarct and being managed for carcinoma rectum.

Among other previous cases, Reddy et al⁹ conducted a case report on a male of age 33 years diagnosed with carcinoma rectum who developed neurological symptoms, i.e. dizziness, impaired coordination, headache and double vision.

Hemachudha et al⁵ documented the case of a 68-year-old male diagnosed with advanced cecal adenocarcinoma, who presented with neurological symptoms that began with rigidity, tremor, and difficulty swallowing. In a separate case, Serteser et al¹⁰ reported on a 57-year-old man experiencing a recurrence of right-sided colon cancer, exhibited confusion and loss of speech. In a comparable case, Ziani et al⁸ described a 54-year-old man with gastric adenocarcinoma who experienced an acute behavioral episode marked by the abrupt onset of agitation along with stereotypic movements.

In a case series, Jose et al⁷ detailed three rectal adenocarcinoma patients who developed acute 5-FU neurotoxicity: a 30-year-old male with stage cT3N2M0 disease experienced headache, dysarthria, and dysphagia after chemoradiotherapy; a 34-year-old male presented with dizziness, fatigue, speech disturbances, perioral numbness, and jaw seizures; and a 60-year-old male with pulmonary metastases exhibited encephalopathy, agitation, and disorientation. Notably, two patients manifested focal neurological deficits simulating an acute stroke.

A key diagnostic challenge in this case was the initial resemblance to acute ischaemic stroke—the sudden-onset hemiparesis, dysarthria, and NCCT findings of a right MCA territory infarct were clinically indistinguishable from a thromboembolic event. However, the bilateral and symmetric MRI signal changes, disproportionate to the predominantly unilateral clinical deficit, combined with the temporal relationship to FOLFIRI administration and the known risk of 5-FU neurotoxicity, supported the diagnosis of toxic leukoencephalopathy. The absence of a cardioembolic source on echocardiography and the lack of large vessel occlusion on CT angiography further strengthened this conclusion.

Similar diagnostic difficulties have been described previously. Jose et al⁷ reported patients with gastrointestinal malignancies receiving 5-FU-based chemotherapy who developed acute neurotoxicity, with a median onset of approximately 3 days following infusion. Two patients developed focal neurological deficits closely mimicking acute stroke. MRI with diffusion-weighted imaging (DWI) was able to differentiate and individualise the diagnosis.

Serteser et al¹⁰ described a 57-year-old man with relapsed colon cancer who developed acute confusion and loss of speech 4 days after FOLFIRI and bevacizumab. CT excluded hemorrhage and major territorial infarction, whereas DWI demonstrated bilateral, symmetric white-matter diffusion restriction, supporting toxic leukoencephalopathy. Neurological recovery followed withdrawal of chemotherapy.

Hemachudha et al⁵ reported acute neurological toxicity following infusional 5-FU in a patient with cecal adenocarcinoma, initially raising concern for neuroleptic malignant syndrome. MRI revealed extensive bilateral white-matter abnormalities. The authors emphasized that 5-FU toxicity can produce stroke-like focal deficits and that early MRI is crucial.

Ambreen et al¹¹ similarly reported a young man with colon cancer who developed headache, dizziness, and slurred speech during continuous 5-FU infusion. A primary NCCT was unremarkable, whereas DWI showed widespread, symmetric restricted diffusion involving the deep white matter and corpus callosum. These reports emphasize that a normal early CT does not exclude 5-FU-induced toxic leukoencephalopathy and that DWI/ADC imaging is essential when stroke-like symptoms occur after fluoropyrimidine therapy.

Our case notably showed a wild-type DPYD genotype, with no deficiency detected in the four most commonly tested variants — highlighting that 5-FU neurotoxicity is not solely a pharmacogenomic phenomenon. Non-genetic factors—including cumulative drug exposure, impaired hepatic or renal metabolism, individual pharmacokinetic variability, and as yet uncharacterised metabolic pathways—may independently contribute to drug accumulation and toxicity. Phenotypic assessment of DPYD enzyme activity, such as plasma uracil levels or the uracil breath test, may identify DPYD deficiency not captured by standard genotyping panels and may provide complementary information in such cases.

Jose et al⁷ performed DPYD analysis in three of five patients. Two tested patients had wild-type results, whereas one harbored a pathogenic heterozygous mutation involving exons 2, 13, and 18. Despite the presence of a genetic defect in one patient, it was emphasized that central neurotoxicity may not consistently correlate with DPD deficiency and suggested that cumulative drug exposure, metabolic disturbances, dehydration, renal dysfunction, and altered 5-FU catabolism may contribute to toxicity. This series provides evidence for both genetically susceptible and genetically negative cases.

In contrast, Hemachudha et al⁵ did not perform DPYD testing because genetic analysis was unavailable at their institution. Their case therefore could not be categorized genetically, and the proposed mechanisms centered on non-genetic metabolic disturbances, including altered thiamine metabolism, TCA-cycle suppression, hyperlactatemia, metabolic acidosis, dehydration, and malnutrition.

Reddy et al.⁹ reported a patient with rectal carcinoma who developed acute 5-FU-associated leukoencephalopathy. DPYD genotyping was not performed; therefore, the patient's underlying pharmacogenomic susceptibility could not be established. This case therefore complements the present findings by demonstrating that DPYD status is not routinely part of 5-FU-induced leukoencephalopathy. Ziani et al. also reported no DPYD genetic testing, with the proposed mechanisms involving abnormal 5-FU catabolism and host-specific pharmacokinetic factors.

Ambreen et al¹¹ described acute toxic leukoencephalopathy without prior DPYD pharmacogenomic profiling and highlighted prolonged infusional exposure and individual metabolic factors. Likewise, Serteser et al¹⁰ did not report DPYD mutation analysis; neurological recovery followed withdrawal of FOLFIRI and supportive management.

So this shows the relevance of integrating both pharmacogenomic and phenotypic assessment strategies into pre-treatment evaluation. As oncology advances toward precision medicine, such individualised risk stratification is critical to optimising chemotherapy safety and improving patient outcomes.

Limitations

This case report is limited in certain aspect as it is based on a single patient, the findings cannot be

generalized to all patients who receive 5-FU. DPYD testing was restricted to commonly screened variants and thus cannot exclude other genetic or functional abnormalities that affect DPD activity. Detailed pharmacokinetic evaluation was not done.

Conclusion

5-FU-induced toxic leukoencephalopathy is a rare but potentially severe complication that can closely mimic acute ischemic stroke - this case underscores the need to consider chemotherapy-induced neurotoxicity when acute deficits follow 5-FU treatment, especially with bilateral, symmetric, non-territorial white-matter changes on MRI. Normal early CT should not rule out the diagnosis; and though DPYD abnormalities may increase susceptibility, neurotoxicity can still occur with a wild-type result for commonly tested variants. Early recognition, prompt 5-FU discontinuation, supportive care, and timely MRI are key to diagnosis and neurological recovery.

References

1. Sung H, Filho AM, Laversanne M, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. *CA Cancer J Clin*. 2026;76(4):e70090. doi: 10.3322/caac.70090.
2. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, et al. Electronic address: clinicalguidelines@esmo.org. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(1):10-32. doi: 10.1016/j.annonc.2022.10.003.
3. Peng C, Saffo S, Oberstein PE, Shusterman M, Thomas C, Becker DJ, et al. Omission of 5-fluorouracil bolus from multidrug regimens for advanced gastrointestinal cancers: a multicenter cohort study. *J Natl ComprCancNetw*. 2024;22(8):521–7.
4. Ho TT, Smith DM, Aquilante CL, Cicali EJ, El Roubi N, Hertz DL, et al. A guide for implementing DPYD genotyping for systemic fluoropyrimidines into clinical practice. *Clin Pharmacol Ther*. 2025;117(5):1194-208. doi: 10.1002/cpt.3567.
5. Hemachudha P, Rattanawong W, Pongpitakmetha T, Phuenpathom W. Fluorouracil-induced leukoencephalopathy mimicking neuroleptic malignant syndrome: a case report. *J Med Case Rep*. 2023;17(1):86. doi: 10.1186/s13256-023-03814-3.
6. Supreeth RN, Hingmire S, Joshi A. 5-Fluorouracil-induced leukoencephalopathy: report of two cases and review of literature. *Ind J*

5-Fluorouracil-Induced Neurotoxicity Presenting as Acute Toxic Leukoencephalopathy in a Patient with Metastatic Carcinoma Rectum: A Case Report

- Med Paediatr Oncol. 2024;45(6):546–549. doi: 10.1055/s-0044-1779488.
7. Jose N, Joel A, Selvakumar RJ, Ramireddy J, John AO, Georgy JT, et al. Diagnosis and management of 5-fluorouracil (5-FU)-induced acute leukoencephalopathy: lessons learnt from a single-centre case series. J Egypt Natl Canc Inst. 2022;34(1):22. doi: 10.1186/s43046-022-00117-4.
 8. Ziani H, Nasri S, Kamaoui I, Skiker I. 5-Fluorouracil-induced acute leukoencephalopathy: Case report and literature review. Radiol Case Rep. 2024;19(7):2801-3. doi: 10.1016/j.radcr.2024.03.064.
 9. Reddy N, Garachh M, Reddy MJ. A case of 5 fluorouracil induced leukoencephalopathy in a patient on treatment for carcinoma rectum. Int J Sci Res. 2016;5(2):126-7.
 10. Serteser E, Öztaş A, Karaçin C, Yoloğlu Z. FOLFIRI-bevacizumab-induced acute toxic leukoencephalopathy. J Oncol Pharm Pract. 2023;29(6):1516-9. doi: 10.1177/10781552231178680.
 11. Ambreen A, Naveed MA, Javed K, Naeem MQ, Chaudhry N. 5-fluorouracil-induced acute toxic leukoencephalopathy: a rare adverse effect and its early detection on MRI. Cureus. 2025;17(11):e98058. doi: 10.7759/cureus.98058.