

5-Fluorouracil-induced severe hyperlactatemic encephalopathy during chemotherapy for advanced colorectal cancer: Case reports and literature review

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Received June 30, 2026; Accepted October 16, 2026

DOI: 10.3892/etm.2026.13346

Abstract. 5-Fluorouracil (5-FU) is a key drug in the treatment of advanced colorectal cancer (CRC). Although 5-FU is generally well tolerated, a small subset of patients may experience life-threatening neurotoxicity. Among these complications, 5-FU-induced encephalopathy accompanied by severe hyperlactatemia is a particularly serious metabolic emergency. Impaired drug clearance, especially due to underlying renal insufficiency, may substantially increase this risk. In the present study, the cases of three patients with advanced CRC who developed acute, severe impairment of consciousness 48 h after receiving 5-FU-based chemotherapy were retrospectively reviewed. Clinical presentations ranged from aphasia and confusion to deep coma. All patients exhibited marked hyperlactatemia, with peak blood lactate levels of 18.0, 18.19 and 15.56 mmol/l for Cases 1, 2 and 3, respectively. A total of two patients had marked baseline renal impairment (one with chronic kidney disease, the other with end-stage renal disease on maintenance hemodialysis). Neuroimaging (CT/CT perfusion/CT angiography/MRI) excluded acute cerebrovascular events in all cases. Chemotherapy was immediately discontinued and intensive supportive care was initiated. For the patient with anuric renal failure, early continuous venovenous hemofiltration was initiated. All three patients achieved complete neurological recovery and

normalization of metabolic parameters. Notably, the hemodialysis-dependent patient subsequently underwent successful 5-FU rechallenge using a 50% dose reduction combined with prophylactic post-chemotherapy hemodialysis, without recurrence of neurotoxicity. 5-FU-induced severe hyperlactatemic encephalopathy is a potentially fatal oncological emergency. Underlying renal impairment may lead to the accumulation of toxic metabolites. For patients presenting with extreme hyperlactatemia (>10 mmol/l) and profound impairment of consciousness, early initiation of continuous renal replacement therapy may be an effective strategy to resolve neurological dysfunction. In patients with end-stage renal disease requiring subsequent fluoropyrimidine therapy, substantial dose reduction combined with prophylactic hemodialysis may offer a feasible rechallenge approach. Furthermore, clinicians must consider genetic mutations related to hepatotoxicity and nephrotoxicity. Evaluation of these organ-vulnerability genes before chemotherapy warrants further clinical investigation to prevent severe toxicity.

Introduction

Colorectal cancer (CRC) remains one of the most prevalent and lethal malignancies worldwide. Recent real-world epidemiological studies have shown that, although the overall incidence rate in the elderly population has decreased due to the wider use of screening, the incidence and related mortality of early-onset CRC (age, <50 years) are significantly increasing, and long-term survival remains a major challenge (1). In this context, 5-fluorouracil (5-FU)-based regimens continue to serve as the backbone of both adjuvant and palliative chemotherapy for this disease (2,3). While 5-FU is generally well tolerated, with myelosuppression, mucositis and gastrointestinal toxicity being the most common adverse effects, a small proportion of patients may develop acute, life-threatening neurotoxicity, a condition termed fluorouracil-induced encephalopathy (FIE). Large-scale real-world pharmacovigilance data indicate that such marked metabolic encephalopathy can trigger severe brain edema and elevated intracranial pressure, potentially resulting in an irreversible deep coma or even brain herniation. FIE typically manifests as the sudden onset of confusion,

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Key words: 5-fluorouracil, lactic acidosis, metabolic encephalopathy, continuous renal replacement therapy, renal insufficiency, colorectal cancer

lethargy, speech disturbance or altered muscle tone. Its clinical presentation is highly nonspecific, often mimicking acute cerebrovascular events or other metabolic encephalopathies, which poses substantial challenges for early recognition (4). Pharmacovigilance data suggest that the intensive care unit admission rate for FIE can reach 57%, with a mortality rate of ~17% (5).

Pathophysiologically, >80% of administered 5-FU is catabolized by dihydropyrimidine dehydrogenase (DPD, encoded by the *DPYD* gene) in the liver (6). While FIE is occasionally complicated by hyperammonemia, metabolic encephalopathy accompanied by severe type B lactic acidosis is considered a more serious condition (7). The underlying mechanism is thought to involve inhibition of mitochondrial aconitase by 5-FU metabolites (particularly fluoroacetate), which disrupts the tricarboxylic acid (TCA) cycle and forces a metabolic shift toward anaerobic glycolysis, resulting in excessive lactate production (8).

Emerging evidence suggests that the risk of this metabolic crisis may reflect impairment of both pathways of drug clearance: Reduced DPD enzymatic activity [due to *DPYD* polymorphisms such as *DPYD**2A (c.1905+1G>A)] impairs hepatic catabolism of the parent drug, while coexisting renal insufficiency compromises the excretion of downstream water-soluble toxic metabolites such as fluoro-beta-alanine (FBAL) (9). However, clinical experience in managing the most severe presentations—patients with blood lactate exceeding 15 mmol/l and profound coma—remains limited, and the role of early continuous renal replacement therapy (CRRT) in this context has not been well characterized.

The present study reported three cases of 5-FU-induced severe hyperlactatemic encephalopathy (peak lactate 15.56–18.19 mmol/l), including two patients with significant baseline renal impairment, all of whom achieved complete neurological recovery. The clinical features, the role of CRRT in acute management and a successful rechallenge strategy in a hemodialysis-dependent patient were discussed to provide information on the early identification and treatment of this rare but potentially fatal complication.

Case report

The clinical timeline, serial blood lactate levels and Glasgow Coma Scale (GCS) scores (10) of all three patients treated at Sir Run Run Shaw Hospital (Hangzhou, China) are summarized in Table I.

Case 1: Severe hyperlactatemia in a patient with chronic kidney disease (CKD). In April 2026, a 75-year-old man was admitted for palliative chemotherapy for rectal cancer with liver metastases. The patient's baseline renal function indicated CKD, with a serum creatinine of 201 $\mu\text{mol/l}$ (normal range, 57–111 $\mu\text{mol/l}$). A genetic test report from October 2020 indicated that the patient's tumor was wild-type for *KRAS*, *NRAS* and *BRAF*. In addition, the patient's *DPYD* genotype was wild-type [rs3918290 (C/C)]. However, ~48 h after receiving the 5-FU, leucovorin and irinotecan (FOLFIRI) plus cetuximab regimen (standard dose of 2,400 mg/m²), the patient suddenly developed nausea and vomiting, followed by rapid neurological deterioration, manifesting as ataxia, limb

tremors, aphasia and lethargy. The patient became comatose (GCS score of 6), underwent emergency endotracheal intubation and was transferred to the intensive care unit (ICU) in April 2026. Arterial blood gas analysis revealed severe lactic acidosis: Blood lactate was 11.92 mmol/l (normal range, 0.5–2.2 mmol/l) at 56 h post-chemotherapy, which subsequently rose to a peak of 18.0 mmol/l at 60 h, with a pH of 7.378 and a base excess of -8.3 mmol/l (normal range, -2 to +3 mmol/l). Head CT and CT perfusion (CTP) imaging showed no acute hemorrhage or extensive ischemia (Fig. 1A). A diagnosis of 5-FU-induced metabolic encephalopathy was established. Following immediate drug discontinuation and aggressive fluid resuscitation, the metabolic disturbances resolved rapidly. Repeat arterial blood gas analysis the next day showed that lactate had decreased to 2.8 mmol/l. The patient was successfully extubated and transferred back to the general ward. Following the completion of radiotherapy in May 2026, the patient has been under regular outpatient follow-up at our institution. The surveillance protocol includes monthly evaluations of serum tumor markers and imaging assessments every three months; to date, there has been no evidence of tumor progression.

Case 2: Deep coma in a hemodialysis patient treated with CRRT. A 66-year-old woman with widely metastatic colon cancer had uremia and had received regular hemodialysis for 14 years. The modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX6) chemotherapy regimen (standard dose of 2,400 mg/m²) was administered during the interdialytic period. At ~48 h after chemotherapy administration, the patient suddenly became deeply comatose (GCS score of 3) with flaccid paralysis of all four limbs [muscle strength grade 0 (11)] and was transferred to the ICU in March 2026. Laboratory tests revealed severe decompensated metabolic acidosis: pH 7.181 (normal range, 7.35–7.45), peak blood lactate 18.19 mmol/l and HCO_3^- 11.1 mmol/l (normal range, 18–23 mmol/l). Emergency head CTP imaging and plain head CT (Fig. 1B) ruled out intracranial hemorrhage and large-vessel lesions. Additionally, a bedside ambulatory electroencephalogram (AEEG) showed moderate-to-marked abnormalities, characterized by a lack of background alpha waves and continuous, diffuse moderate-to-high amplitude polymorphic theta (4–7 Hz) and delta (2–3 Hz) waves, consistent with severe metabolic encephalopathy (12) (Fig. 2A). Considering that the anuric renal failure drastically exacerbated the accumulation of metabolites, the ICU initiated CRRT at 60 h (12 h after coma onset) using a continuous venovenous hemofiltration (CVVH) modality. Within 3 h after starting CRRT (at 63 h), the patient's level of consciousness improved markedly, with the GCS score rising rapidly from 3 to 12. Following discussion with the patient's family and obtaining informed consent, CRRT was temporarily paused due to financial constraints. The medical team closely monitored the patient's clinical status. Blood lactate levels remained stable between 65 and 117 h (ranging from 1.3 to 4.1 mmol/l). By 123 h, the GCS score reached 15 (fully awake), and the patient was transferred out of the ICU in a stable condition.

Notably, ~1 month after the patient's initial encephalopathy crisis (April 2026), the patient required further chemotherapy due to tumor progression. The medical team planned a cautious

Table I. Clinical timeline, serial blood lactate levels and GCS scores of the three patients.

A, Case 1			
Time post-chemo, h	Clinical event	Blood lactate, mmol/l	GCS score
0	Initiation of chemotherapy (baseline)	-	-
41	Nausea, vomiting and limb tremors	-	-
56	Sudden onset of coma, ICU admission and intubation	11.92	6
60	-	18	-
70	Fully awake and extubated	2.8	15
78	-	3.5	-
83	-	0.9	15
92	-	0.9	-
96	Transferred out of ICU	-	15
B, Case 2			
Time post-chemo, h	Clinical event	Blood lactate, mmol/l	GCS score
0	Initiation of chemotherapy (baseline)	-	-
24	Continuous chemotherapy	-	-
48	Sudden onset of deep coma	18.19	3
60	Initiation of CRRT (CVVH mode)	9.8	-
63	Cessation of CRRT	4.9	12
72	Continuous monitoring	3.8	15
96	Continuous monitoring	2.5	15
117	Continuous monitoring	1.4	15
123	Fully awake and extubated	-	15
C, Case 3			
Time post-chemo, h	Clinical event	Blood lactate, mmol/l	GCS score
0	Initiation of chemotherapy (baseline)	-	-
48	Sudden onset of coma, unresponsive, ICU admission	15.56	7
52	-	14	-
57	-	6	-
61	-	3.6	14
69	-	2.6	-
72	Conscious, transferred out of ICU	-	15

The normal range for blood lactate is 0.5-2.2 mmol/l. The GCS ranges from 3-15 with a score <9 indicating a comatose state. Hyphens (-) indicate that the corresponding data were not applicable or not recorded at that specific time-point. GCS, Glasgow Coma Scale; ICU, intensive care unit; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration.

rechallenge strategy. In April 2026, the patient received mFOLFOX6 at a 50% dose reduction. Simultaneously, in collaboration with the nephrology department, early prophylactic post-chemotherapy hemodialysis was scheduled. Under strict clinical monitoring, the patient remained fully conscious (GCS score maintained at 15) throughout the chemotherapy process, without any recurrence of neurological abnormalities. A follow-up arterial blood gas analysis on the day after chemotherapy showed that the blood lactate level was within the normal range (1.94 mmol/l), with a pH of 7.31. Laboratory and clinical data confirmed that this strategy of substantial

dose reduction combined with prophylactic dialysis successfully prevented the re-accumulation of toxic metabolites. The patient ultimately completed chemotherapy without complications and was discharged safely. In June 2026, the patient developed multiple pelvic metastases, which were confirmed by biopsy as originating from the primary CRC. The patient was subsequently lost to follow-up at our hospital and is currently receiving palliative care at a local institution.

Case 3: Encephalopathy with severe hyperlactatemia. A 74-year-old woman with a history of cerebral infarction

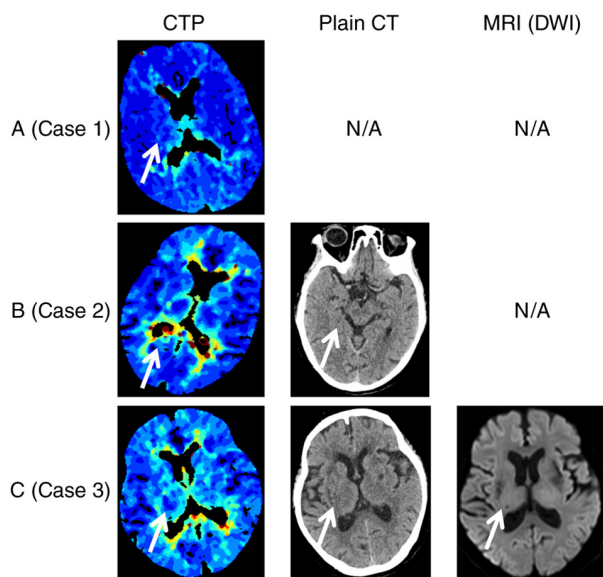


Figure 1. Neuroimaging evaluations for Cases 1-3 during the acute encephalopathy crisis. (A) Case 1: CTP. Plain CT and MRI were not performed in this case due to the emergency setting. (B) Case 2: Plain CT and CTP. (C) Case 3: Plain CT, MRI (DWI) and CTP. The available imaging across all three cases demonstrates relatively symmetric and normal cerebral blood flow without significant perfusion deficits or acute large-area infarction. White arrows indicate areas of normal brain parenchyma and baseline perfusion on CTP, and the absence of restricted diffusion or acute ischemic changes on plain CT and MRI, which collectively aided in excluding acute ischemic stroke. CTP, computed tomography perfusion; N/A, not available; DWI, diffusion-weighted imaging.

was admitted with rectal cancer and abdominopelvic metastases following surgery in January 2026. After receiving a reduced-dose FOLFIRI regimen (2,000 mg/m², ~80% of the standard dose) combined with bevacizumab, the patient suffered sudden loss of consciousness and increased systemic muscle tone 48 h post-chemotherapy in January 2026. Blood gas analysis showed a markedly elevated lactate level of 15.56 mmol/l. Emergency head CTP (Fig. 1C) demonstrated no significant perfusion deficits. Furthermore, MRI/diffusion-weighted imaging and plain head CT (Fig. 1C) were also performed, which definitively excluded acute cerebral ischemia. In addition, bedside AEEG revealed the disappearance of background alpha waves, which were replaced by diffuse medium-to-high-amplitude polymorphic theta and delta waves occurring in prolonged runs, providing definitive electrophysiological evidence for severe toxic-metabolic encephalopathy (12) (Fig. 2B). After chemotherapy was discontinued and continuous intravenous hydration was administered to promote metabolism, the patient's consciousness fully recovered within 24 h. A repeat arterial blood gas analysis showed a lactate level of 2.6 mmol/l and a pH of 7.446, with the acid-base imbalance corrected. During the latest outpatient follow-up in July 2026, the patient was undergoing antineoplastic treatment with a regimen consisting of irinotecan, raltitrexed and bevacizumab.

A retrospective review of the patient's medical records revealed that a pharmacogenomic panel conducted in December 2025 (prior to chemotherapy) showed wild-type genotypes for common DPYD variants [including rs3918290

(CC)]. Despite the absence of pathogenic DPYD mutations and the preemptive 20% dose reduction in the chemotherapy regimen, the patient still developed a life-threatening hyperlactatemic encephalopathy crisis. This underscores the rapid onset and unpredictability of 5-FU neurotoxicity in susceptible elderly patients. However, the same report revealed high-risk variants in other genes: ERCC1 [rs11615 (A/G)] and GSTP1 [rs1695 (A/A)] (13). These genetic variants are associated with increased nephrotoxicity and severe overall drug toxicity. This suggests that the patient's organs were highly vulnerable to chemotherapy before treatment.

Discussion

The most striking feature of this case series is the severe hyperlactatemia that suddenly emerged 48 h after 5-FU chemotherapy. In previous reports, peak lactate levels in 5-FU-related lactic acidosis generally range from 5-10 mmol/l (7,14). However, the lactate peaks in the patients of the present study reached 15.56-18.19 mmol/l and were accompanied by severely impaired neurological function. According to current biochemical models, degradation products of 5-FU (particularly FBAL) have potential mitochondrial toxicity and can inhibit key enzymes of the TCA cycle (8). The anaerobic conversion of intracellular pyruvate to lactate and the depletion of energy substrates in the central nervous system (7) may together underlie the sudden deep coma and diffuse brain electrophysiological abnormalities (such as the slow-wave presentation on the AEEG of Case 3) observed in the present cases.

Given the critical clinical importance of rapid lactate monitoring, emerging diagnostic technologies, such as near-infrared fluorescent nanoprobes for highly sensitive L-lactate detection in CRC, may offer valuable translational potential in the future (15).

The terminal toxic metabolites of 5-FU, including FBAL and its downstream product fluoroacetate, depend on renal excretion (16). Of the three patients in this series, two had significant baseline renal impairment: Case 1 had chronic kidney disease with a serum creatinine of 201 μ mol/l, and Case 2 had end-stage renal disease requiring maintenance hemodialysis. In both patients, the DPYD genotype was wild-type and DPD activity was therefore predicted to be normal. This suggests that renal impairment alone may be an important independent risk factor: When renal excretion is impaired, normal hepatic catabolism appears insufficient to prevent accumulation of water-soluble metabolites, which is consistent with the delayed hyperlactatemic episodes occurring 48-72 h after administration that were observed in Cases 1 and 2, and with previous reports of 5-FU encephalopathy in patients with end-stage renal disease (16,17) (Table II).

Genetic factors beyond DPYD may also modulate individual susceptibility. Case 3 carried variants in ERCC1 (rs11615) and GSTP1 (rs1695) in addition to a wild-type DPYD genotype, and developed severe encephalopathy despite a 20% preemptive dose reduction. ERCC1 participates in nucleotide excision repair, and GSTP1 participates in the detoxification of reactive oxygen species; reduced activity of either may increase the susceptibility of renal tubular cells to cytotoxic

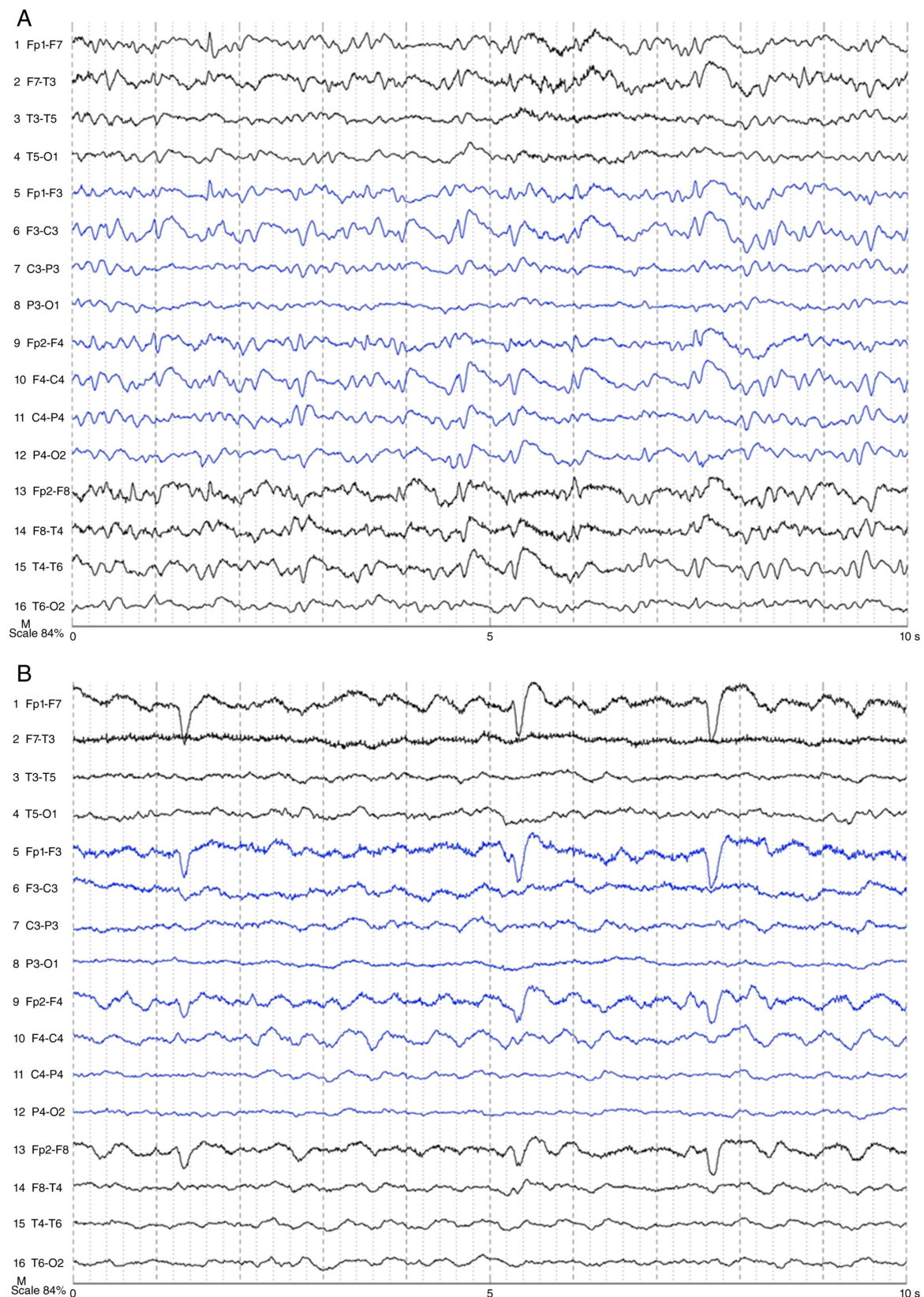


Figure 2. Ambulatory electroencephalogram tracings during the acute encephalopathy crisis. (A) Case 2 and (B) Case 3. Both tracings demonstrate moderate-to-marked abnormalities, characterized by the disappearance of normal background alpha rhythms and the continuous, diffuse firing of moderate-to-high amplitude polymorphic theta and delta slow waves, indicating severe toxic-metabolic encephalopathy.

stress. These variants may therefore have contributed to the acute kidney injury observed after chemotherapy, which may in turn have impaired metabolite clearance (13). It should be

emphasized that this association is observational, is based on a single patient and requires validation in larger cohorts before any causal role can be assigned.

Table II. Comparison of clinical characteristics between the present cases and 5-FU-induced hyperlactatemic encephalopathy reported in the literature over the past 5 years.

First author, year	Age/sex	Primary tumor	Baseline renal function	Chemotherapy regimen	5-FU dose	Onset time	Peak blood lactate, mmol/l	Neurological presentation	Interventions and prognosis	Recovery time	(Refs.)
Asano <i>et al.</i> , 2024	51/M	Rectal cancer	AKI (Cr 3.36 mg/dl)	FOLFIRI-like regimen	NA	48 h post-dose	>30.0	Consciousness disorder	CHDF (CRRT)/recovered	NA	(9)
Jin <i>et al.</i> , 2024	67/M	Rectal cancer	Normal	5-FU continuous infusion	High-dose continuous	40 h post-infusion	9.1	Loss of consciousness, limb stiffness	Drug cessation, supportive care/recovered	~12 h	(14)
Salimi <i>et al.</i> , 2026	60+/F	Colon cancer	Normal	5-FU + radiotherapy	Continuous infusion	60-68 h post-infusion	5.4	Confusion, delayed response	Lactulose, hydration/recovered	8-24 h	(7)
Case 1 (present)	75/M	Rectal cancer	CKD (Cr 201 μ mol/l)	FOLFIRI + Cetuximab	2400 mg/m ² (standard)	~48 h post-dose	18.0	Ataxia, aphasia, lethargy	Drug cessation, hydration, intubation/recovered	~24 h (next day)	-
Case 2 (present)	66/F	Colon cancer	Uremia (maintenance HD)	mFOLFOX6	2400 mg/m ² (standard)	48 h post-chemo	18.19	Deep coma (GCS 3)	Drug cessation, CVVH (CRRT)/recovered	~75 h	-
Case 3 (present)	74/F	Rectal cancer	Mild impairment (eGFR 82 ml/min)	FOLFIRI + Bevacizumab	2000 mg/m ² (80% standard)	48 h post-chemo	15.56	Unresponsive, severe consciousness disorder, AEEG: Diffuse slow waves	Drug cessation, hydration/recovered	Within 24 h	-

Recovery time refers to the duration from the onset of neurological symptoms to complete recovery. 5-FU, 5-fluorouracil; Cr, creatinine; AKI, acute kidney injury; CKD, chronic kidney disease; CHDF, continuous hemodiafiltration; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; GCS, Glasgow Coma Scale; AEEG, ambulatory electroencephalogram; HD, hemodialysis; eGFR, estimated glomerular filtration rate; M, male; F, female; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; FOLFIRI, fluorouracil, leucovorin and irinotecan.

Prevention in such patients should not rely on DPYD genotyping alone. International guidelines recommend pretreatment screening for DPYD variants such as DPYD*2A before fluoropyrimidine-based therapy (18), and genotype-guided dose adjustment reduces the risk of severe toxicity. Because dosing based on body surface area does not capture interindividual variability in drug exposure, therapeutic drug monitoring of the 5-FU area under the curve may provide an additional safeguard, although it was not available during the crises described here (19).

Regarding the therapeutic role of extracorporeal clearance in acute 5-FU encephalopathy, the following should be considered. For mild to moderate 5-FU encephalopathy, drug discontinuation and intensive hydration are usually effective (14). In patients with renal insufficiency, severe lactic acidosis (>10 mmol/l) and oliguria or anuria, however, fluid resuscitation alone is unlikely to provide adequate clearance and carries a substantial risk of volume overload. In such life-threatening presentations (Case 2: pH 7.18, GCS 3), early initiation of CRRT appeared to be beneficial through two mechanisms.

First, CRRT provides direct extracorporeal clearance of the parent drug and its neurotoxic metabolites. 5-FU is a small molecule (130 Da) with high water solubility and low plasma protein binding ($\sim 10\%$), and FBAL and fluoroacetate also have low molecular weights. These properties make them amenable to blood purification, and previous pharmacokinetic work indicates that hemodialysis efficiently removes circulating 5-FU and FBAL.

Second, CRRT corrects the acid-base and energy disturbances. Lactate is a small molecule (~ 90 Da) and is removed across the extracorporeal circuit, while bicarbonate-containing replacement fluid corrects the extracellular acidosis. In Case 2, lactate fell and the GCS score improved within a short period after CVVH was started. This temporal association is consistent with a causal contribution of extracorporeal clearance, although causality cannot be established from a single case.

Regarding prophylactic renal replacement therapy before rechallenge, blood purification also has a preventive role. In patients with end-stage renal disease who require further fluoropyrimidine therapy, initiating hemodialysis soon after chemotherapy, combined with a substantial dose reduction, may prevent metabolite accumulation. Case 2 illustrates this approach: The 5-FU dose was reduced by 50% and prophylactic hemodialysis was scheduled after each cycle; no neurological toxicity recurred (17).

In terms of differential diagnosis of hyperammonemic encephalopathy, the following may be considered. Among the central nervous system toxicities induced by 5-FU, hyperammonemic encephalopathy is the most commonly reported subtype in previous literature (20). From a pathophysiological perspective, hyperammonemia and hyperlactatemia share a common mechanism of metabolic blockade: Toxic intermediate metabolites of 5-FU (particularly fluoroacetate) can strongly inhibit aconitase, a key enzyme in the mitochondrial TCA cycle, leading to a marked reduction in the production of intracellular adenosine triphosphate (ATP). Because the urea cycle in the liver (the process of converting ammonia to urea) is highly ATP-dependent, energy depletion inevitably leads to disruption of the urea cycle, subsequently triggering abnormally elevated blood ammonia (21). Concurrently, the

blockade of the TCA cycle forces cellular metabolism to shift towards anaerobic glycolysis, causing a massive conversion of pyruvate to lactate.

However, the clinical phenotype of the cases in this series is more consistent with an encephalopathy crisis driven primarily by severe lactic acidosis. Typical patients with 5-FU-induced hyperammonemia mostly exhibit mild to moderate elevations in plasma lactate (usually <8 – 10 mmol/l) and rarely present with profound decompensated acidemia (pH <7.2) (22). By contrast, the patients of the present study (especially those with underlying end-stage renal disease or CKD) experienced markedly impaired excretion of toxic metabolites, causing a nearly complete blockade of mitochondrial function in target organs (particularly the energy-demanding central nervous system). To maintain basic survival, central neurons were forced to rely entirely on anaerobic metabolism, thereby producing a degree of hyperlactataemia rarely reported in this setting (peak blood lactate levels as high as 15.56–18.19 mmol/l).

This marked acidic shift in the intracellular and extracellular microenvironment not only directly interferes with normal neurotransmitter transmission and ion channel function (23) but is also a direct biochemical cause of sudden aphasia, ataxia and even a deep coma with a GCS of 3. Therefore, although the possibility of concurrent hyperammonemia during the disease course in the patients of the present study cannot be entirely ruled out, the severe hyperlactatemia and its resulting fatal acid-base imbalance are clearly the principal mechanisms underlying the clinical phenotype and prognosis of the crises in this series.

For patients with CRC who have experienced severe 5-FU encephalopathy but still require further treatment, the following options of subsequent antineoplastic treatment should be considered. In terms of emergency antidotal therapy and dose-reduced rechallenge, in patients who develop early, life-threatening 5-FU toxicity within 96 h of administration, the Food and Drug Administration-approved antidote uridine triacetate should be administered as early as possible, since it competitively inhibits incorporation of toxic metabolites into RNA and reduces mortality in fulminant fluoropyrimidine toxicity (24). When the original regimen cannot be replaced and neurological recovery is complete, rechallenge with a substantially reduced dose is feasible: A French national survey of 5-FU encephalopathy supports dose reduction rather than permanent withdrawal (20), and Case 2 shows that a 50% dose reduction combined with prophylactic post-chemotherapy hemodialysis allowed the patient with uremia to complete further cycles safely.

In terms of switching to regimens with alternative metabolic pathways, in patients with confirmed pathogenic DPYD variants, or in those who remain intolerant to 5-FU despite dose reduction, re-exposure to fluoropyrimidines should be avoided and a regimen that does not depend on DPD metabolism should be selected. Raltitrexed, a thymidylate synthase inhibitor, has antitumor activity comparable to 5-FU in CRC and bypasses the DPD pathway entirely, making it an appropriate intravenous alternative (25). Trifluridine/tipiracil (TAS-102) is also not degraded by DPD and provides an additional oral option for such patients (26).

Several limitations of the present study warrant consideration. First, this is a retrospective case series of only three patients without a control group, so the observations cannot

establish the efficacy of any specific intervention. Second, 5-FU therapeutic drug monitoring was not available during the acute crises; systemic accumulation of toxic metabolites therefore remains an inference rather than a demonstrated mechanism, and the pathogenic role of renal impairment, although biologically plausible and supported by the clinical courses, cannot be proven from these data. Third, the proposed association between non-DPYD variants (ERCC1 rs11615 and GSTP1 rs1695) and organ vulnerability is strictly observational; mechanistic validation in larger cohorts is required before a causal relationship can be considered. Finally, the strategy of dose reduction combined with prophylactic hemodialysis is described in only one patient and should not be considered established practice.

In conclusion, 5-FU-induced severe hyperlactatemic encephalopathy is a challenging oncological emergency. Underlying renal insufficiency may be an important risk factor for the accumulation of toxic metabolites. For patients presenting with significantly elevated blood lactate (>10 mmol/l) combined with severe impairment of consciousness, early identification, immediate drug discontinuation and prompt intervention with CRRT are effective strategies for improving clinical outcomes. Furthermore, clinicians must look beyond standard DPYD screening. Attention should also be paid to genetic mutations associated with severe hepatotoxicity and nephrotoxicity (such as ERCC1 and GSTP1). Evaluation of these 'organ-vulnerability' genes warrants further validation in larger cohorts, especially for elderly patients, to prevent acute organ failure and subsequent severe metabolic decompensation.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 82504210).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YJ drafted the manuscript and collected the clinical data. XX and WZ assisted with the literature review and data analysis. DM contributed to the clinical management of the patients. DX and DW conceptualized the study, supervised the clinical care and critically revised the manuscript. DX and DW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (approval no. 2026-2383-01). The requirement of written informed consent to participate was waived by

the Ethics Committee due to the retrospective nature of this case series.

Patient consent for publication

Written informed consent for publication of clinical details and images was obtained from the patients or their legal guardians.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (Gemini Advanced; Google LLC; <https://gemini.google.com/>) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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