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Diffuse Cytotoxic Lesions of the Corpus Callosum Following Folinic Acid, Fluorouracil, and Oxaliplatin (FOLFOX) Chemotherapy: A Case Report

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Abstract

Cytotoxic lesions of the corpus callosum (CLOCCs) are a neuroradiological pattern associated with diverse conditions, including drug-related toxicity. Although commonly centered in the splenium, lesions may extend throughout the corpus callosum and into adjacent white matter. We report the case of a 38-year-old woman with metastatic colonic adenocarcinoma who developed acute confusion and visual disturbances four days after initiation of her first cycle of folinic acid, fluorouracil, and oxaliplatin (FOLFOX). Neurological examination revealed right-eye exotropia without motor or sensory deficits. Laboratory investigations, including serum ammonia, were unremarkable. Brain magnetic resonance imaging (MRI) demonstrated bilateral, symmetric T2-weighted/fluid-attenuated inversion recovery (FLAIR) hyperintensities involving the entire corpus callosum and periventricular white matter, with restricted diffusion, reduced apparent diffusion coefficient (ADC), and no contrast enhancement. These findings supported a diagnosis of FOLFOX-associated CLOCCs, potentially related to 5-fluorouracil (5-FU) neurotoxicity. Complete neurological recovery occurred within 24 hours, and follow-up MRI at one month showed complete resolution. FOLFOX was subsequently resumed with a 25% reduction in the 5-FU dose and close monitoring, without neurological recurrence or other observed complications. This case illustrates that extensive callosal involvement can accompany a rapidly reversible neurological episode. The favorable outcome following reduced-dose reintroduction demonstrates that permanent treatment discontinuation was not required in this patient and supports an individualized approach to subsequent chemotherapy.

Categories: Neurology, Radiology, Oncology
Keywords: 5-fluorouracil, cloccs, cytotoxic lesions of the corpus callosum, encephalopathy, folfox, magnetic resonance imaging

Introduction

The corpus callosum is the largest commissural white matter structure in the human brain, providing the main anatomical pathway for interhemispheric communication. It comprises four segments - the rostrum, genu, body, and splenium - and facilitates the transfer and integration of sensory, motor, cognitive, and visuospatial information between the cerebral hemispheres. The splenium predominantly connects posterior cortical regions and contributes to the integration of visual and other sensory information [1].

Cytotoxic lesions of the corpus callosum (CLOCCs) represent a distinctive neuroradiological pattern associated with a wide range of clinical conditions, including infections, metabolic disturbances, seizures, malignancies, and drug-related toxicity. Although these lesions typically involve the splenium, they may extend to the entire corpus callosum and adjacent white matter. Magnetic resonance imaging (MRI) characteristically reveals T2-weighted and fluid-attenuated inversion recovery (FLAIR) hyperintensities associated with restricted diffusion and decreased apparent diffusion coefficient (ADC) values. These lesions are often reversible, although their clinical significance and outcome depend on the underlying etiology [2,3].

FOLFOX is a widely used chemotherapy regimen for colorectal and other gastrointestinal malignancies. It combines folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin, which exert their antineoplastic effects through complementary mechanisms. Although oxaliplatin is primarily associated with peripheral sensory neuropathy, fluoropyrimidine-based chemotherapy may occasionally cause central nervous system complications, including encephalopathy, seizures, and white matter abnormalities [4,5].

CLOCCs have also been described in association with 5-FU-containing chemotherapy regimens; however, this manifestation remains rare, and its underlying mechanisms are not fully understood [6,7].

We report a case of diffuse cytotoxic lesions of the corpus callosum following the first cycle of FOLFOX chemotherapy in a patient with metastatic colonic adenocarcinoma. This observation highlights the

importance of recognizing this uncommon imaging pattern in patients presenting with neurological symptoms during cancer treatment and considering chemotherapy-related neurotoxicity in the differential diagnosis.

Case Presentation

A 38-year-old woman with moderately differentiated colonic adenocarcinoma, liver metastases, and peritoneal carcinomatosis started systemic chemotherapy with FOLFOX. The regimen consisted of intravenous oxaliplatin (85 mg/m²) and folinic acid (leucovorin; 400 mg/m²), each infused over two hours, followed by an intravenous bolus of 5-fluorouracil (5-FU; 400 mg/m²) and a continuous intravenous infusion of 5-FU (2,400 mg/m²) over 46 hours.

Four days after initiation of the first chemotherapy cycle, the patient developed an acute, mild alteration in mental status, characterized by confusion and disorientation to time and place, with a Glasgow Coma Scale score of 14/15 (E4V4M6), lasting approximately one hour, without loss of consciousness. This was accompanied by a brief episode of blurred vision without diplopia. There was no reported fever or seizure activity, and no clinical signs of raised intracranial pressure were observed. The patient was hemodynamically stable, with normal vital signs. She was afebrile, with normal respiratory effort and oxygen saturation. Cardiac and pulmonary examinations were unremarkable. Neurological examination showed no facial asymmetry, motor weakness, or sensory deficits; coordination and gait were normal. Ocular examination revealed exotropia of the right eye without nystagmus or ptosis. The pupils were equal in size and reactive to light, and convergence was preserved. Visual acuity was maintained, with no visual field deficits on confrontation testing. The remainder of the cranial nerve examination was normal. Laboratory investigations were unremarkable, including serum electrolytes, renal and hepatic function tests, vitamin levels, a complete blood count with platelet count, C-reactive protein, and serum ammonia levels (Table *1*). Testing for dihydropyrimidine dehydrogenase (DPD) deficiency was not performed.

Laboratory parameter	Patient's value	Reference range	Unit
White blood cell count	8.0	4.0-10.0	$\times 10^3/\mu L$
Red blood cell count	4.90	3.90-5.50	$\times 10^6/\mu L$
Hemoglobin	14.0	13.0-17.0	g/dL
Hematocrit	42.2	41.0-53.0	%
Neutrophil count	4.8	1.5-7.5	$\times 10^3/\mu L$
Lymphocyte count	2.1	1.5-4.0	$\times 10^3/\mu L$
Monocyte count	0.5	0.1-0.8	$\times 10^3/\mu L$
Platelet count	244	150-450	$\times 10^3/\mu L$
C-reactive protein (CRP)	3.6	<5.0	mg/L
Sodium	140	135-145	mmol/L
Potassium	4.20	3.70-5.30	mmol/L
Chloride	106	95-110	mmol/L
Blood glucose	0.98	0.7-1.1	g/L
Urea	3.7	2.5-6.4	mmol/L
Creatinine	7	6-13	mg/L
Alanine aminotransferase (ALT)	36	<40	U/L
Aspartate aminotransferase (AST)	26	<35	U/L
Alkaline phosphatase	40	32-92	U/L
Total bilirubin	12	3-12	mg/L
Plasma ammonia	13	11-48	µmol/L
Vitamin B12	380	187-800	pg/mL
Vitamin B9	11	3.1-20	ng/mL

TABLE 1: Laboratory findings following the onset of neurological symptoms and corresponding reference ranges.

Brain MRI demonstrated extensive, bilateral, and symmetric T2-weighted and FLAIR hyperintensities involving the entire corpus callosum, with extension into the periventricular white matter of both cerebral hemispheres. The abnormalities exhibited a striking mirror-image distribution across the midline. The affected regions showed restricted diffusion, with high signal intensity on diffusion-weighted imaging (DWI) and corresponding low signal on ADC maps (Figure *1*).

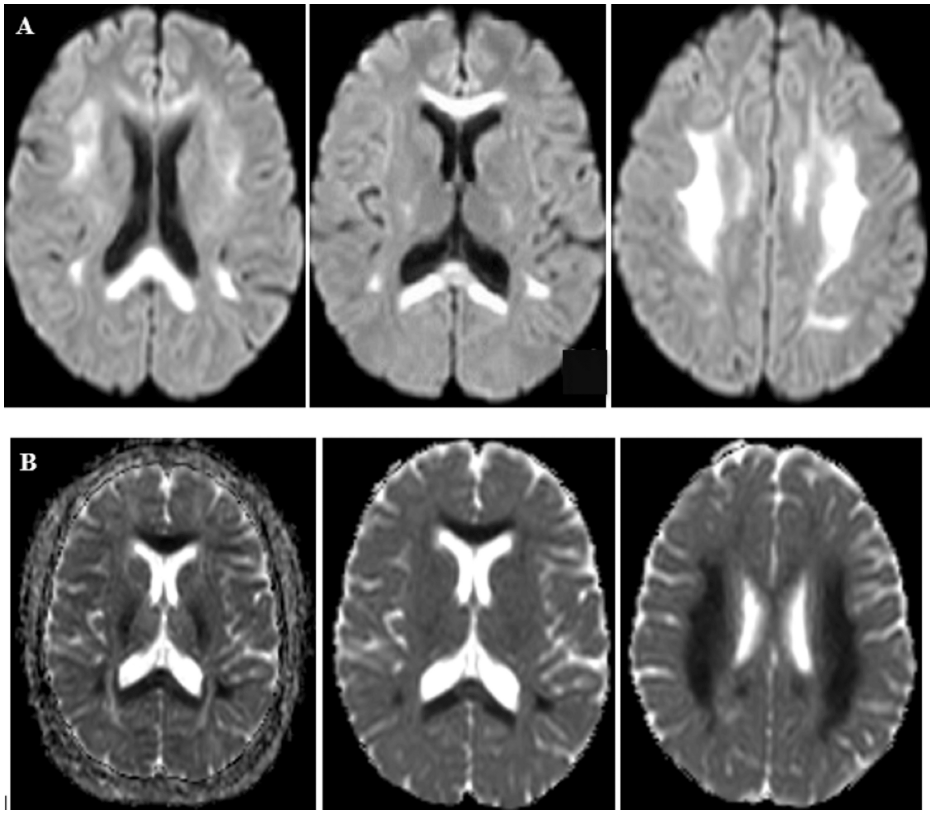


FIGURE 1: Initial brain MRI.

(A) Axial diffusion-weighted images demonstrate symmetric hyperintensity involving the corpus callosum and extending into the bilateral periventricular white matter. (B) Corresponding apparent diffusion coefficient (ADC) maps show reduced signal in the same regions. The imaging pattern is consistent with diffuse cytotoxic lesions of the corpus callosum (CLOCCs) with associated periventricular white matter involvement.

MRI, magnetic resonance imaging

No contrast enhancement was observed following gadolinium administration. The symmetric, nonterritorial distribution and lack of enhancement favored a toxic injury pattern rather than an ischemic or neoplastic process. Taken together, the MRI findings and temporal relationship with chemotherapy supported a diagnosis of diffuse FOLFOX-associated CLOCCs, potentially related to 5-FU neurotoxicity. Neither electroencephalography (EEG) nor cerebrospinal fluid analysis was performed, given the early clinical improvement observed during the MRI examination, subsequent complete resolution of neurological symptoms within 24 hours, and imaging findings supporting the diagnosis of CLOCCs.

Management consisted of hydration and close clinical and neurological monitoring on a standard inpatient ward. No thiamine or antiseizure medication was administered, and intensive care was not required. Complete neurological recovery occurred within 24 hours, including resolution of confusion and visual disturbances. No interhemispheric disconnection syndrome was observed. Follow-up brain MRI at one month demonstrated complete resolution of the callosal and periventricular abnormalities, with no residual signal changes (Figure *2*).

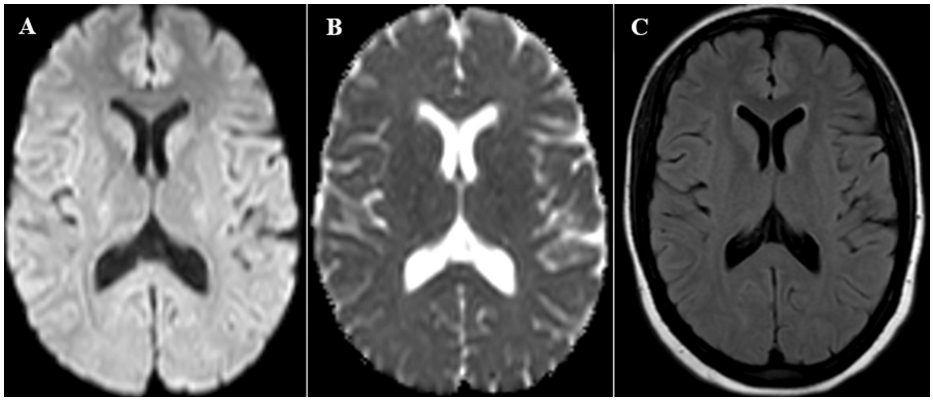


FIGURE 2: Follow-up brain MRI at one month.

(A) Axial diffusion-weighted imaging, (B) apparent diffusion coefficient map, and (C) FLAIR imaging demonstrate complete resolution of the previously observed callosal and periventricular abnormalities.

FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

Chemotherapy was resumed one month after the neurological episode, following clinical recovery and normalization of the follow-up brain MRI. Given the oncological need to continue treatment and the lack of an available alternative, the oncology team elected to reintroduce the regimen with a 25% reduction in the 5-FU dose, guided by previously reported cases. Chemotherapy was subsequently administered every two weeks, with no recurrence of neurological symptoms during six months of follow-up. Thus, in this patient, the neurological episode did not necessitate permanent discontinuation of FOLFOX, and reduced-dose reintroduction was well tolerated.

Discussion

Several overlapping terms have been used for transient callosal abnormalities, including transient splenial lesions, mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), and reversible splenial lesion syndrome (RESLES). MERS emphasizes an encephalitic or encephalopathic presentation with a generally favorable course, whereas RESLES emphasizes the reversible imaging abnormality across a broader range of clinical settings [8,9].

The term CLOCCs provides a more inclusive designation because the lesions are not invariably confined to the splenium, associated with mild symptoms, or fully reversible [2,3]. This terminology is appropriate in our patient, whose abnormalities extended throughout the corpus callosum and into the periventricular white matter. CLOCCs represent a shared imaging response rather than a condition with a single cause. Moors et al. identified infectious, toxic, metabolic, vascular, traumatic, and neoplastic associations in a systematic review of 324 publications and 1,353 patients [3].

The proposed pathophysiology of CLOCCs involves cytokine-mediated inflammatory signaling and glutamate excitotoxicity, leading to intracellular water accumulation and cytotoxic edema [2]. Following a systemic or cerebral insult, inflammatory signaling involving interleukin-1, interleukin-6, and tumor necrosis factor may promote endothelial dysfunction and blood-brain barrier disruption. Altered glutamate-glutamine cycling, ATP depletion, and excitotoxic signaling may subsequently disturb ionic and water homeostasis, leading to cytotoxic edema [9]. The abundance of glutamate-responsive receptors in callosal tissue, particularly the splenium, may explain its susceptibility and the shared imaging pattern across different triggers [2,10].

Fluorouracil-associated neurotoxicity may involve impaired drug clearance due to reduced DPD activity, thiamine-related disturbances, and metabolite-induced disruption of energy metabolism [5]. In particular, fluoroacetate-mediated inhibition of the Krebs cycle provides a biochemical explanation for impaired cellular energy production [11]. Hyperammonemia may accompany this process but is not required: Acharya et al. reported reversible splenial injury with normal ammonia levels and subsequently normal DPD testing [6]. Similarly, Natarajan et al. described severe 5-FU-associated neurotoxicity with diffusion restriction involving the corpus callosum and other brain regions despite the absence of detectable DPD-related polymorphisms. This further supports the occurrence of fluoropyrimidine neurotoxicity without evidence of a recognized DPD-related genetic predisposition [12].

MRI is the principal modality for identifying and following CLOCCs. Typical features include T2/FLAIR hyperintensity and DWI hyperintensity with corresponding ADC reduction, and usually absent enhancement [2,3]. Three principal distributions have been described: a small central splenial lesion; splenial involvement

extending laterally through callosal fibers into adjacent white matter; and posterior involvement extending anteriorly along the corpus callosum [2].

The abnormalities in our patient represented an extensive pattern involving the entire corpus callosum, with bilateral extension into the periventricular white matter. Their strikingly symmetric, mirror-image distribution, restricted diffusion, and absence of enhancement were characteristic of diffuse toxic injury involving the corpus callosum and white matter. Complete disappearance on follow-up MRI further supported the diagnosis of CLOCCs. González and Garnica identified whole-callosal and periventricular involvement in 13 of the 123 pediatric patients reviewed [13], showing that this distribution belongs to the broader anatomical spectrum.

The symmetric, nonterritorial appearance and complete resolution differed from a typical ischemic lesion. Demyelination, inflammatory disease, and neoplastic infiltration remain imaging differential considerations; their assessment depends on the overall distribution, enhancement, clinical course, and follow-up rather than on one isolated feature [2,3,9].

CLOCC presentations may include altered consciousness, confusion, seizures, headache, dizziness, ataxia, and visual symptoms. Manifestations often reflect the broader systemic or neurological disturbance rather than isolated loss of callosal function [8,9]. Lu et al. described diverse symptoms, including visual disturbances, dizziness, seizures, and confusion, in 15 adults [14].

No interhemispheric disconnection syndrome was observed despite involvement of the entire corpus callosum. Such syndromes are generally absent in CLOCCs, unlike some destructive callosal lesions. The transient nature of cellular injury offers a possible explanation for preserved or rapidly restored interhemispheric function [2,8,10].

Complete clinical recovery within 24 hours was notable given the extensive MRI abnormalities. Clinical and imaging recovery need not coincide: in our patient, the follow-up MRI documented full resolution at one month, whereas Kopyta et al. described persistent abnormalities at three months despite neurological improvement in an adolescent with Epstein-Barr virus infection [15]. Prognosis therefore needs to be interpreted in the context of the underlying condition.

FOLFOX was resumed with a 25% reduction in the 5-FU dose and close clinical monitoring. Subsequent treatment was not accompanied by recurrent neurological symptoms or other observed complications. The episode did not constitute an absolute contraindication to further FOLFOX in this individual, and permanent discontinuation was not required.

Acharya et al. reported reintroduction of fluorouracil at a lower dose without similar symptoms during the rechallenge cycle [6]. Yamada et al. described a 20% reduction after hyperammonemic encephalopathy, with no recurrence during 34 courses over 19 months [16]; this was a related encephalopathic presentation rather than MRI-confirmed CLOCCs. Conversely, the patient reported by Soares discontinued FOLFIRINOX and received gemcitabine [7]. These experiences support individualized decisions incorporating recovery, imaging evolution, oncological benefit, and available alternatives. Initial recovery in our patient preceded dose modification; the absence of recurrence indicates a favorable outcome following subsequent reintroduction.

This report has the inherent limitations of a single case. Causality between fluorouracil and the callosal lesions cannot be established with certainty: a contribution from oxaliplatin, the underlying malignancy, or other concurrent metabolic stressors cannot be fully excluded, although the temporal relationship, normal laboratory findings, rapid reversibility, and complete imaging resolution favor a toxic etiology. Tolerance of dose-reduced rechallenge in one patient should not be generalized, and decisions about re-exposure should remain individualized.

Conclusions

Diffuse CLOCCs with periventricular white matter involvement may occur shortly after FOLFOX chemotherapy and resolve rapidly despite extensive MRI abnormalities. In this patient, complete neurological recovery occurred within 24 hours, and follow-up MRI at one month confirmed full resolution. Reintroduction of FOLFOX with a 25% reduction in the 5-FU dose was well tolerated, with no neurological recurrence or other observed complications during subsequent treatment. This case demonstrates that permanent discontinuation was not required and highlights the value of individualized treatment decisions following clinical recovery.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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