

Severe Ifosfamide-Associated Encephalopathy Requiring Mechanical Ventilation With Gradual Neurological Recovery During Methylene Blue Therapy: A Case Report

Yash Ranga

yashranga2002@gmail.com

Jawaharlal Nehru Medical College

Mohammad Alshaer

Cleveland Clinic

Venkata Peddi

Cleveland Clinic

Case Report

Keywords: Ifosfamide-induced neurotoxicity, encephalopathy, methylene blue, delayed response, case report

Posted Date: March 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9097783/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at SN Comprehensive Clinical Medicine on May 25th, 2026. See the published version at <https://doi.org/10.1007/s42399-026-02443-3>.

Abstract

Background:

Ifosfamide-induced encephalopathy (IIE) is a well-recognized complication of ifosfamide therapy, typically presenting as mild and reversible neurocognitive dysfunction. Severe, life-threatening cases requiring mechanical ventilation are rare and pose significant diagnostic challenges in complex oncology patients with multiple competing etiologies for altered mental status. Furthermore, evidence guiding the optimal dosing, duration, and safety monitoring of methylene blue therapy in refractory presentations remains extremely limited.

Case Description:

A 44-year-old man with metastatic retroperitoneal spindle cell sarcoma and normal baseline renal and hepatic function was admitted for chemotherapy. His clinical picture was confounded by a recent complicated urinary tract infection treated with ciprofloxacin, which precipitated mild prodromal delirium. However, within 24 hours of receiving combination chemotherapy with doxorubicin and ifosfamide (cumulative ifosfamide dose ~16.6 g), he experienced an abrupt, catastrophic neurological decline culminating in coma and requiring mechanical ventilation. Non-contrast brain computed tomography was unremarkable. Cerebrospinal fluid analysis revealed mild lymphocytic pleocytosis; however, comprehensive infectious, autoimmune, and paraneoplastic evaluations were negative, rendering immune checkpoint inhibitor encephalopathy from prior pembrolizumab exposure less likely. Continuous electroencephalography (EEG) demonstrated diffuse generalized delta–theta slowing with frontal predominance. Given the precipitous post-infusion decline, severe IIE was diagnosed. Following mandatory screening confirming the absence of glucose-6-phosphate dehydrogenase (G6PD) deficiency and concomitant serotonergic medications, intravenous methylene blue (50 mg every 8 hours) was initiated. Despite no neurological improvement during the first 72 hours, the extended 5-day therapeutic course was temporally associated with progressive clinical recovery and parallel EEG background normalization, ultimately resulting in successful extubation.

Conclusions:

This case illustrates a rare, life-threatening presentation of IIE requiring mechanical ventilation and demonstrates that neurological recovery following methylene blue therapy may be delayed in severe cases. Prolonged methylene blue administration, guided by clinical course and serial EEG monitoring, may be beneficial when early response is absent. Increased recognition of severe IIE and further study of treatment duration and response predictors are warranted.

Introduction

Ifosfamide is a widely used alkylating chemotherapeutic agent with established efficacy in the treatment of sarcomas, lymphomas, and testicular malignancies. Neurotoxicity is a well-recognized adverse effect [with a prevalence of upto 40% (1)] of ifosfamide therapy and is primarily attributed to neurotoxic metabolites such as chloroacetaldehyde. Clinical manifestations span a broad spectrum, ranging from mild, transient cognitive impairment to severe encephalopathy (1).

Although most cases of ifosfamide-induced encephalopathy (IIE) are self-limited and resolve with supportive care, severe presentations requiring intensive care support are rare and underreported. These cases are characterized by rapid neurological deterioration, including coma and the need for mechanical ventilation. Furthermore, they pose substantial diagnostic and therapeutic challenges, particularly in complex oncology patients where multiple potential etiologies for altered mental status—such as recent infections, critical illness-related factors, and prior exposure to immune checkpoint inhibitors (e.g., pembrolizumab)—may act as confounding factors that contribute to the encephalopathy or alter recovery dynamics.

Methylene blue has been described as a therapeutic option for IIE; however, available evidence is limited to case reports and small case series. The optimal dosing, duration, and discontinuation criteria for methylene blue remain undefined, which limits clinical reproducibility. While many published cases describe rapid neurological improvement following methylene blue administration, data addressing delayed or prolonged responses in severe, refractory presentations remain sparse.

We report a case of life-threatening severe encephalopathy in a patient with metastatic spindle cell sarcoma shortly after ifosfamide administration. The clinical course was marked by rapid neurological decline requiring mechanical ventilation and a delayed clinical and electroencephalographic recovery observed during extended methylene blue therapy. This case highlights the challenges of diagnosing IIE amidst competing clinical confounders and explores the temporal association of prolonged methylene blue administration in severe presentations.

Case Description

A 44-year-old man with a history of hypertension, alcohol use disorder, and a pulmonary embolism two months prior (on anticoagulation with apixaban) was diagnosed with biopsy-confirmed metastatic stage IV spindle cell sarcoma of the retroperitoneum with extensive pulmonary metastases. Tumor burden resulted in left ureteric obstruction, necessitating percutaneous nephrostomy placement for renal drainage. Baseline neurological examination was normal. Notably, baseline laboratory evaluation demonstrated normal renal function, normal hepatic transaminases, and normal serum albumin levels, which are critical to note as renal impairment and hypoalbuminemia are established risk factors for ifosfamide-induced neurotoxicity.

Initial staging computed tomography (CT) demonstrated a large retroperitoneal mass occupying much of the lower abdomen and pelvis, with diffuse bilateral pulmonary metastases. The patient was initiated on pembrolizumab approximately two weeks after diagnosis, with plans for combination chemotherapy with doxorubicin and ifosfamide three weeks later. Palliative radiotherapy was initiated concurrently.

Approximately one week before chemotherapy initiation, the patient developed a complicated urinary tract infection (UTI) and was treated with oral ciprofloxacin. During this period, family members noted increasing somnolence and intermittent visual hallucinations. While these prodromal neuropsychiatric symptoms likely represented a multifactorial delirium—potentially exacerbated by the complicated UTI and fluoroquinolone-related neurotoxicity—the patient remained conversational and able to follow commands. He subsequently developed shortness of breath and hemoptysis; repeat chest CT demonstrated progression of pulmonary metastatic disease, and anticoagulation was held.

During hospitalization, the patient's mental status progressively worsened. Within 24 hours of receiving his first cycles of intravenous ifosfamide (a cumulative dose of 16.6 g over two days) and doxorubicin, he experienced an abrupt, precipitous neurological deterioration progressing to unresponsiveness. He was intubated for airway protection and transferred to the intensive care unit (ICU). Non-contrast CT imaging of the brain was unremarkable. A brain magnetic resonance imaging (MRI) scan, which would have offered higher sensitivity for detecting white matter changes or inflammatory findings, could not be obtained due to the patient's clinical instability; this reliance on CT alone represents a limitation in our diagnostic workup.

The initial differential diagnosis included ifosfamide-induced encephalopathy (IIE), immune checkpoint inhibitor-associated encephalopathy (secondary to pembrolizumab), infectious meningoencephalitis, and medication-induced delirium. Lumbar puncture revealed mild lymphocytic pleocytosis (8 cells/mm³, 82% lymphocytes) with normal protein and glucose. Cerebrospinal fluid (CSF) cultures, herpes simplex virus PCR, autoimmune encephalitis panel, and paraneoplastic panel were negative. Routine laboratory evaluation demonstrated no significant metabolic derangements (normal electrolytes, ammonia, thyroid function, vitamin B12, and lactate).

To evaluate for nonconvulsive status epilepticus (NCSE) in the setting of unexplained coma, continuous bedside electroencephalography (EEG) was initiated. The EEG demonstrated diffuse generalized delta–theta slowing with bilateral frontal predominance. While there were intermittent features concerning for possible subclinical seizure activity, these findings were formally adjudicated and did not meet the established Salzburg criteria for NCSE.

During his ICU course, the patient developed severe agitation and hyperactive delirium requiring sedation. Propofol infusion was discontinued due to hypotension, and sedation was transitioned to dexmedetomidine. Persistent agitation was managed with adjunctive quetiapine, with gradual improvement over 48 hours. Given the irritable EEG findings, intravenous levetiracetam was initiated prophylactically.

Pembrolizumab-associated encephalopathy was considered less likely given the short interval from initiation and the absence of supportive MRI or CSF findings. Furthermore, the negative autoimmune and paraneoplastic studies reduced the likelihood of alternative inflammatory etiologies. Ultimately, while the complicated UTI and ciprofloxacin may have lowered his neurological reserve, the abrupt and catastrophic deterioration immediately following ifosfamide infusion prioritized severe IIE as the primary diagnosis.

Intravenous methylene blue was initiated at a dose of 50 mg every 8 hours. Prior to administration, the patient's medication profile was screened to ensure the absence of concomitant serotonergic medications (including interacting opioids) to mitigate the risk of serotonin syndrome. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an absolute contraindication to methylene blue due to the risk of severe hemolysis, was ruled out. Throughout the 5-day therapeutic course, the patient was closely monitored for adverse effects, including routine checks of hemolysis markers and awareness of potential pulse oximetry artifacts, with no adverse events observed.

No significant neurological improvement was observed during the first 72 hours of methylene blue therapy; however, continued administration over the 5-day course was associated with delayed but meaningful clinical improvement and progressive normalization of the EEG background activity. The patient regained sustained

responsiveness, with intermittent hyperactive delirium that resolved approximately one week after methylene blue initiation. Following a successful spontaneous breathing trial, the patient was extubated and transferred to the solid tumor oncology service for continued management.

Time Point	Event	Outcome
Baseline	HTN, alcohol use disorder, prior PE on apixaban	Neurologically normal
Diagnosis	Stage IV spindle cell sarcoma	Pulmonary metastases; ureteric obstruction
Staging	CT chest/abdomen/pelvis	Large retroperitoneal mass; diffuse lung disease
Early care	Percutaneous nephrostomy	Renal decompression
~2 w post-dx	Pembrolizumab + radiotherapy	Planned doxorubicin/ifosfamide
~1 w pre-chemo	UTI → ciprofloxacin	Somnolence, hallucinations
Pre-chemo	Dyspnea, hemoptysis	CT: metastatic progression; anticoagulation held
Chemo Day 0	Ifosfamide + doxorubicin	Acute encephalopathy (<24 h)
ICU Day 1	Intubation; CT brain	No acute findings
ICU Day 1–2	LP, EEG, labs	Mild pleocytosis; EEG diffuse slowing; workup negative
ICU course	Delirium, agitation	Dexmedetomidine, quetiapine, levetiracetam
ICU Day ~3	Methylene blue started	Gradual neurologic recovery
Days 4–7	Clinical improvement	EEG normalized; delirium resolved
Recovery	Extubation, ICU discharge	Transferred to oncology

Discussion

Ifosfamide-induced encephalopathy (IIE) is a recognized adverse effect of ifosfamide therapy, affecting up to 10–30% of treated patients. Clinical manifestations range from mild cognitive impairment and behavioral changes to seizures, coma, and respiratory failure. Although most reported cases are transient and self-limited, severe presentations requiring intensive care support are uncommon and remain underrepresented in the literature. Established risk factors for IIE include renal impairment, hypoalbuminemia, hepatic dysfunction, prior cisplatin therapy, and pelvic masses causing urinary tract obstruction. While our patient had a pelvic mass and ureteric obstruction, his baseline renal, hepatic, and synthetic functions were normal prior to admission, making his rapid, severe decline particularly notable.

The neurotoxicity of ifosfamide is primarily mediated by its hepatic metabolite chloroacetaldehyde (CAA), a small lipophilic molecule that readily crosses the blood–brain barrier. CAA exerts neurotoxic effects through several converging mechanisms. At the cellular level, it disrupts mitochondrial oxidative phosphorylation by

interfering with the electron transport chain, resulting in impaired adenosine triphosphate generation and neuronal energy failure. This effect is compounded by the depletion of intracellular glutathione, which diminishes neuronal resilience to oxidative stress. In addition, CAA alters central neurotransmitter signaling, particularly dopaminergic and GABAergic pathways, which likely underlies the agitation, hallucinations, delirium, and fluctuating levels of consciousness observed in IIE (1,3). Importantly, neurotoxicity is not prevented by mesna, as mesna does not neutralize CAA or other neurotoxic metabolites, in contrast to its protective role against hemorrhagic cystitis (1).

Diagnostic evaluation of suspected IIE is highly challenging due to the significant overlap with alternative etiologies frequently encountered in complex oncology patients. Differentiating IIE from immune checkpoint inhibitor–associated encephalopathy, infectious meningoencephalitis, and medication-induced delirium is an increasingly relevant clinical dilemma. In this case, the patient’s pre-chemotherapy somnolence and hallucinations were likely multifactorial, representing a delirium exacerbated by a complicated urinary tract infection and potential fluoroquinolone-related neurotoxicity. However, immune-mediated encephalopathy typically presents with progressive symptoms, inflammatory cerebrospinal fluid (CSF) profiles, and specific MRI findings, making it less likely given the abrupt post-ifosfamide deterioration and unremarkable CSF analysis.

Neuroimaging is critical in this workup. While computed tomography (CT) primarily serves to exclude gross structural pathology like hemorrhage or brain metastases, it lacks sensitivity for subtle inflammatory or toxic changes. Our reliance on non-contrast CT imaging due to the patient’s clinical instability represents an important limitation. Magnetic resonance imaging (MRI) is the modality of choice; although often normal in IIE, it can reveal rare but characteristic subtle abnormalities, such as reversible restricted diffusion or T2/FLAIR hyperintensities in the bilateral thalami and basal ganglia, and is superior for ruling out posterior reversible encephalopathy syndrome (PRES) (4).

Electroencephalography (EEG) plays a vital role in both the diagnosis and longitudinal assessment of IIE, particularly in severe or fluctuating cases where continuous EEG is indicated to evaluate for nonconvulsive status epilepticus. Typical EEG findings include diffuse generalized slowing in the theta to delta frequency range, often with frontal predominance, consistent with a toxic–metabolic encephalopathy (5). Serial EEG monitoring provides significant prognostic value, as electrophysiologic improvement has been shown to closely parallel clinical recovery.

The management of IIE is largely supportive and begins with the immediate discontinuation of ifosfamide to prevent further accumulation of neurotoxic metabolites; rechallenge is generally not recommended (1). Deliriogenic medications, particularly benzodiazepines, should be avoided. Antipsychotic agents such as quetiapine or low-dose haloperidol may be used judiciously for the management of hyperactive delirium. In highly refractory or life-threatening cases, adjunctive therapies such as empiric thiamine supplementation or even renal replacement therapy (hemodialysis) have been occasionally utilized to rapidly clear toxic metabolites, though standard guidelines remain absent.

Methylene blue has been utilized as a targeted antidote for IIE (1,6,7). It functions as an alternative electron acceptor within the mitochondrial electron transport chain, bypassing the CAA-induced blockade to restore

oxidative phosphorylation. Furthermore, it inhibits monoamine oxidase activity—potentially reducing the formation of neurotoxic aldehyde metabolites—and modulates nitric oxide–mediated neuronal signaling (1,6). However, the evidence supporting methylene blue remains strictly limited to case reports and small series, restricting the strength of treatment recommendations. The optimal dosing, duration, and timing of administration in severe cases are not well defined.

Crucially, methylene blue carries significant safety considerations. Because it is a potent monoamine oxidase inhibitor, it can precipitate fatal serotonin syndrome if co-administered with serotonergic agents, including certain opioids and antidepressants. It is also strictly contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of severe hemolytic anemia. Therefore, rigorous screening for interacting medications, confirmation of G6PD status, and vigilant monitoring for hemolysis and pulse oximetry artifacts (false desaturations) are mandatory during therapy.

In most published reports, neurological improvement following methylene blue is observed within 24 to 48 hours, with treatment limited to one to three days (1,6,7). In contrast, our patient required a prolonged five-day course, demonstrating delayed but sustained clinical and electrographic recovery. While this suggests that extended therapy may be required to overcome a high neurotoxic metabolite burden in severe presentations, we acknowledge that this represents a temporal association rather than definitive causation. The self-limiting natural history of IIE, the resolution of concurrent systemic confounders, and the inherent limitations of a single-case observation preclude broad generalizations.

This case contributes to the medical literature by detailing a rare, life-threatening presentation of IIE requiring mechanical ventilation, while emphasizing the diagnostic utility of serial EEG and highlighting the safe use of an extended methylene blue regimen. Further prospective studies and multi-institutional registries are necessary to define optimal methylene blue dosing parameters, identify predictors of prolonged recovery, and establish standardized treatment guidelines for severe ifosfamide-induced neurotoxicity.

Conclusion and Take-Away Points

This case illustrates a rare, life-threatening presentation of severe encephalopathy temporally associated with ifosfamide administration, requiring mechanical ventilation and prolonged intensive care support. Diagnosing severe ifosfamide-induced encephalopathy (IIE) in complex oncology patients demands a rigorous diagnostic approach to exclude compounding clinical factors, including concurrent infections, immune checkpoint inhibitor toxicity, and medication-induced delirium.

While delayed neurological and electroencephalographic recovery in this patient was temporally associated with a prolonged, five-day course of methylene blue, the single-case nature of this observation and the inherently fluctuating, self-limiting potential of IIE preclude definitive causal conclusions. Nevertheless, this case suggests that extended methylene blue administration may be safely considered in severe, refractory presentations. Crucially, if methylene blue is utilized, rigorous pre-treatment screening for G6PD deficiency and concomitant serotonergic medications is mandatory to prevent life-threatening hemolytic or serotonergic complications.

Finally, serial continuous EEG monitoring serves as an indispensable tool in the ICU setting, not only to rule out nonconvulsive status epilepticus but also to longitudinally track objective electrophysiologic recovery in patients with severe, undifferentiated toxic-metabolic encephalopathies. Early recognition, exhaustive exclusion of alternative etiologies, and response-guided, multidisciplinary intensive care management are critical to optimizing outcomes in severe chemotherapy-induced neurotoxicity.

Declarations

-Ethics approval and consent to participate: N/A

-Consent to publish: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

-Availability of data and materials: Originally made by the author.

-Competing interests: NIL

-Funding: No Funding was received

-Authors' contributions:

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

Concept and design: Yash Ranga, Mohammad Alshaer, Venkata Peddi

Acquisition, analysis, or interpretation of data: Yash Ranga, Mohammad Alshaer, Venkata Peddi

Drafting of the manuscript: Yash Ranga, Mohammad Alshaer, Venkata Peddi

Critical review of the manuscript for important intellectual content: Yash Ranga, Mohammad Alshaer, Venkata Peddi

Supervision: Venkata Peddi

-Acknowledgements: Not Applicable.

References

1. Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prové A, Vermorken JB. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer*. 2000;82(2):291–294. doi:10.1054/bjoc.1999.0917.
2. Feng S, Coward J, McCaffrey E, Couchner J, Kalokerinos P, O'Byrne K. Pembrolizumab-induced encephalopathy: a review of neurological toxicities with immune checkpoint inhibitors. *J Thorac Oncol*. 2017;12(11):1626–1635. doi:10.1016/j.jtho.2017.08.007.

3. Darwich NS, Mustafa I. Encephalopathy associated with ifosfamide use in the treatment of diffuse large B-cell lymphoma. *J Neurol Neurobiol*. 2021;7:174. doi:10.16966/2379-7150.174.
4. Ali Mohamed D, Semedo A, Adeyemi B, et al. Reversible encephalopathy induced by ifosfamide with normal brain imaging. *Glob Pediatr Health*. 2021;8:2333794X211030415. doi:10.1177/2333794X211030415.
5. Gusdon AM, Malani R, Chen X. Clinical and EEG characteristics of ifosfamide-related encephalopathy. *J Clin Neurophysiol*. 2019;36(2):150–154. doi:10.1097/WNP.0000000000000539.
6. Patel PN. Methylene blue for management of ifosfamide-induced encephalopathy. *Ann Pharmacother*. 2006;40(2):299–303. doi:10.1345/aph.1G114.
7. Turner AR, Duong CD, Good DJ. Methylene blue for the treatment and prophylaxis of ifosfamide-induced encephalopathy. *Clin Oncol*. 2003;15(7):435–439. doi:10.1016/S0936-6555(03)00114-6.