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Severe Encephalopathy Associated With Ivermectin Use and Extensive CYP3A4 Inhibition in a Patient Undergoing Self-Directed Treatment for Malignancy

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Abstract

Ivermectin is a semi-synthetic antiparasitic medication approved by the United States Food and Drug Administration (FDA) for treatment of several parasitic infections in humans. Although well tolerated at therapeutic doses, ivermectin toxicity can occur with supratherapeutic exposure and is characterized primarily by gastrointestinal distress, confusion, ataxia, weakness, hypotension, seizures, coma, and in severe cases, death. Ivermectin is primarily metabolized by cytochrome P450 3A4 (CYP3A4), and inhibition of this enzyme can increase serum drug concentrations and the risk of toxicity. We report the case of a 49-year-old man who presented to the emergency department (ED) with altered mental status and seizure-like activity, found to be self-treating colorectal cancer with ivermectin as well as numerous supplements and off-label prescription medications obtained online, the majority of which were known inhibitors of CYP3A4. The patient was admitted to the hospital and remained encephalopathic with gradual improvement in mentation and complete resolution of seizure-like activity over several weeks before being discharged to inpatient rehabilitation. Despite near-therapeutic daily dosing, the combination of chronic exposure and multiple CYP3A4 inhibitors likely led to sustained supratherapeutic ivermectin levels and prolonged encephalopathy. This case underscores the risk of severe drug toxicity from internet-promoted alternative cancer regimens and highlights the need for meticulous documentation of nonprescribed therapies in patients with unexplained neurologic presentations.

Categories: Pharmacology, Emergency Medicine, Oncology
Keywords: altered mental status, cyp3a4 inhibition, cyp3a4 inhibitor, encephalopathy, ivermectin toxicity, overdose, self-treatment

Introduction

Ivermectin is a semi-synthetic antiparasitic agent derived from the avermectin class approved by the United States Food and Drug Administration (FDA) for treatment of intestinal strongyloidiasis and onchocerciasis as well as topically for head lice and rosacea [1]. While generally well tolerated at therapeutic doses typically only a few days long, ivermectin toxicity can occur with supratherapeutic or prolonged exposure and is characterized by gastrointestinal distress as well as neurologic manifestations including confusion, ataxia, seizures, coma, and death [2].

Ivermectin is primarily metabolized by CYP3A4, with minor contributions from CYP3A5 and CYP2C9 [3]. Inhibition of CYP3A4 is proposed to increase systemic ivermectin concentrations and contribute to toxicity. Under normal conditions, central nervous system (CNS) exposure is thought to be limited because ivermectin is a substrate for P-glycoprotein, which restricts penetration across the blood-brain barrier [4]. Prolonged elevated serum ivermectin concentrations may permit increased CNS accumulation and neurotoxicity.

In recent years, ivermectin use outside of approved indications has increased, most notably for the self-treatment of COVID-19 [2,5]. More recently, preclinical studies have suggested potential anticancer properties through several proposed mechanisms, including induction of mitochondrial dysfunction, oxidative stress [6], and disruption of signaling pathways such as Wnt/β-catenin, PI3K/Akt/mTOR, and STAT3 [7]. To date, there is no high-quality clinical evidence supporting ivermectin for malignancy, and regulatory agencies and professional societies discourage its use outside clinical trials.

Although cases of ivermectin toxicity related to inappropriate dosing and off-label use have been reported, prolonged ivermectin-associated encephalopathy in the setting of daily dosing combined with CYP3A4-inhibiting polypharmacy for self-directed cancer treatment, to our knowledge, has not been previously reported. There have been cases of patients taking ivermectin for self-directed COVID-19 treatment, with extensive neurotoxicity reported in those cases [2].

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We report the case of a 49-year-old man with a medical history of colorectal cancer who presented to the ED with altered mental status and seizure-like activity after self-administering ivermectin along with numerous supplements and medications obtained online, many of which are known inhibitors of CYP3A4. The patient remained encephalopathic throughout the month-long hospital admission with gradual improvement in mentation until return to baseline mental status and resolution of neurological abnormalities. This case highlights the importance of obtaining a comprehensive medical history and consideration of chronic toxicity of non-prescribed medications.

Case Presentation

A 49-year-old male with a past medical history significant for hyperlipidemia, hypertension, gout, atopic dermatitis, and recurrent rectal adenocarcinoma status post folinic acid/fluorouracil/oxaliplatin (FOLFOX) therapy and radiotherapy presented to a large-volume urban ED via emergency medical services (EMS) with altered mental status and concerns for seizure-like activity. He had no prior history of seizures, cognitive impairment, or psychiatric disease. According to his wife, the patient was in a normal state of health when he went to sleep the night prior around 21:00. He normally woke up around 04:00; however, on that day, when the wife woke up at 09:00, the patient had not gotten out of bed and was reportedly making odd noises and acting strangely. She immediately contacted EMS.

On arrival to the ED, the patient was hemodynamically stable with an oral temperature of 36.6° C, heart rate of 80 beats/minute, respiratory rate of 22 breaths/minute, blood pressure of 134/113 mmHg, and oxygen saturation of 99% on room air. Electrocardiogram (ECG) demonstrated normal sinus rhythm with a right bundle branch block at a rate of 76 beats/minute without interval abnormalities or ST segment changes.

On physical examination, the patient appeared acutely ill and in distress. He was obtunded, encephalopathic, and not following commands, with a Glasgow Coma Scale (GCS) of 10 (eye opening to painful stimuli, incomprehensible verbal responses, and localization of painful stimuli). He was disoriented and confused. Pupils measured 5 mm bilaterally and were sluggishly reactive to light, with a downward gaze preference. The neck was supple, with full passive flexion and rotation and no nuchal rigidity. The remainder of the examination was unremarkable.

A stroke code was activated with concerns for an intracranial process. Computed tomography (CT) of the head without intravenous (IV) contrast, CT perfusion of the brain with IV contrast, and CT angiogram of the head and neck with IV contrast demonstrated no acute intracranial hemorrhage, no evidence of acute infarct or critical hypoperfusion, and widely patent intracranial, carotid, and vertebral arteries. CT of the thorax, abdomen, and pelvis with IV contrast did not demonstrate any acute pathology.

Initial laboratory evaluation, including complete blood count (CBC), complete metabolic panel (CMP), inflammatory markers, infectious studies, thyroid function, and ammonia, was grossly unremarkable, with only mild fluctuations from normal limits on a handful of values (Table *1*). Serum drug testing was remarkable only for naproxen and caffeine. This drug screen is not completely comprehensive, detecting only drugs within its protocol.

Component	Reference Range	Value
White Blood Cell (k/mcL)	4.0 – 10.8	9.9
Red Blood Cell (M/mcL)	4.60 – 6.00	4.11
Hemoglobin (g/dL)	14.0 – 18.0	13.2
Hematocrit (%)	42.0 – 52.0	39.0
Mean Cell Volume (fL)	80.0 – 100.0	94.9
Mean Cell Hemoglobin (pg)	32.0 – 37.0	32.1
Mean Cell Hemoglobin Concentration (g/dL)	32.0 – 37.0	33.8
Red Cell Distribution Width (%)	11.0 – 16.0	11.6
Platelet (k/mcL)	140 – 400	357
Mean Platelet Volume (fL)	7.4 – 11.0	10.0
Neutrophil Automated Absolute (k/mcL)	1.80 – 7.80	6.25
Lymphopocyte Automated Absolute (k/mcL)	1.00 – 4.00	1.97
Monocyte Automated Absolute (k/mcL)	0.00 – 0.90	1.04

Eosinophil Automated Absolute (k/mcL)	0.00 – 0.50	0.58
Basophil Automated Absolute (k/mcL)	0.00 – 0.20	0.05
Immature Granulocyte Automated Absolute (k/mcL)	0.00 – 0.05	0.05
Immature Granulocyte Automated (%)	0.0 – 0.6	0.5
Nucleated Red Blood Cells Automated (%)	0.0	0.0
Neutrophil Automated (%)	35.0 – 80.0	62.9
Lymphocyte Automated (%)	20.0 – 50.0	19.8
Monocyte Automated (%)	2.0 – 12.0	10.5
Eosinophil Automated (%)	0.0 – 6.0	5.8
Basophil Automated (%)	0.0 – 2.0	0.5
Sodium (mmol/L)	134 – 146	137
Potassium (mmol/L)	3.4 – 5.0	4.0
Chloride (mmol/L)	98 – 112	103
Bicarbonate (mmol/L)	21 – 29	19
Anion Gap (mmol/L)	5 – 14	15
Glucose (mg/dL)	70 – 99	94
Blood Urea Nitrogen (mg/dL)	8 – 20	24
Creatinine (mg/dL)	0.60 – 1.30	0.98
Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	>60	>90
Calcium (mg/dL)	8.6 – 10.4	9.4
Protein Total (g/dL)	6.0 – 8.0	8.2
Albumin (g/dL)	3.5 – 5.2	4.3
Bilirubin Total (mg/dL)	0.2 – 1.0	0.6
Alkaline Phosphatase (U/L)	40 – 129	110
Alanine Aminotransferase (U/L)	0 – 50	32
Aspartate Aminotransferase (U/L)	0 – 50	23
Ammonia (mcmol/L)	0 – 60	12
Magnesium (mg/dL)	1.6 – 2.5	1.8
Lipase (U/L)	<50	25
Activated Partial Thromboplastin Time (s)	24.0 – 34.0	25.8
Prothrombin Time (s)	9.5 – 12.0	10.4
International Normalized Ratio	0.9 – 1.2	1.0
Lactic Acid (mmol/L)	0.0 – 2.0	0.7
Ethanol (mg/dL)	<10	<10
High-Sensitivity Cardiac Troponin T (ng/L)	<22	<6
Triglycerides (mg/dL)	<150	146
Thyroid Stimulating Hormone (mcIU/mL)	0.30 – 5.00	1.73
Venous pH	7.32 – 7.40	7.31
Venous pCO2 (mm/Hg)	38 – 52	48
Venous pO2 (mm/Hg)	24 – 48	25

Venous Oxygen Saturation (%)	65 – 100	40
Base Excess (mmol/L)	−2.0 – 2.0	−2.0
Urine Clarity	Clear	Clear
Urine Specific Gravity	1.002 – 1.030	1.035
Urine pH	6.0 – 8.0	6.0
Urine Glucose (mg/dL)	Negative	Negative
Urine Ketones (mg/dL)	Negative	Negative
Urine Protein (mg/dL)	Negative	Negative
Urine Blood	Negative	Negative
Urine Bilirubin	Negative	Negative
Urine Urobilinogen (mg/dL)	0.2 – 1.0	Negative
Urine Nitrite	Negative	Negative
Urine Leukocyte Esterase	Negative	Negative
Urine White Blood Cells (/HPF)	0 – 5	<1
Urine Red Blood Cells (/HPF)	0 – 3	1
Urine Squamous Epithelial Cells (/HPF)	<20	3
COVID-19 PCR	Not Detected	Not Detected
Influenza A PCR	Not Detected	Not Detected
Influenza B PCR	Not Detected	Not Detected
RSV PCR	Not Detected	Not Detected

TABLE 1: Laboratory tests in the emergency department

PCR: polymerase chain reaction; RSV: respiratory syncytial virus

He was outside the window to receive thrombolytics, and no large-vessel occlusion was identified on CT imaging. With concern for focal motor or nonconvulsive seizures due to witnessed forced downward gaze and abnormal ocular movements without generalized tonic-clonic activity, 2 mg IV lorazepam was administered with cessation of that activity, and 3 g IV levetiracetam was subsequently loaded. Peripheral blood cultures were obtained. He was admitted to the neurological intensive care unit (ICU) for further management in guarded condition.

Shortly after arrival to the neurological ICU, the patient became less responsive with sonorous respirations and a GCS of 6. He was emergently intubated for airway protection and administered an additional 1.5 g of IV levetiracetam. Magnetic resonance imaging (MRI) of the brain with and without contrast, as well as lumbar puncture with cerebrospinal fluid (CSF) analysis, showed no evidence of stroke, intracranial metastasis, infection, or inflammatory CNS disease. The patient's wife reported recent month-long travel to Thailand. Infectious disease service was consulted and, after extensive evaluation, considered an infectious etiology unlikely.

At this time, the patient's wife shared that the patient was taking multiple supplements and off-label prescription medications in an effort to self-treat his colorectal cancer. His regimen, which included ivermectin most recently taken the day before, consisted of at least 21 non-prescribed agents, many of which are known to inhibit CYP3A4 (Table *2*). His wife reported daily ivermectin use of 5 mL of 2 mg/mL solution (10 mg/day, 131 μg/kg/day at a weight of 76.3 kg) for the past two months. The typical therapeutic dose for parasite infection is 150-200 μg/kg/day in one to three-day courses. Chronic daily dosing, in conjunction with multiple proposed CYP3A4 inhibitors, may have led to accumulation beyond typical peak exposures seen with short regimens used to treat parasitic infections. Medical toxicology service was consulted with concern for ivermectin toxicity. Toxicology service noted ivermectin's prolonged half-life of approximately 18 hours and that seizures and encephalopathy are well-described manifestations of toxicity.

CYP3A4 and CYP2C9 Inhibition	CYP3A4 Inhibition	No effect on CYP3A4 or CYP2C9
Cimetidine	Artemisia	Chromium picolinate
		Garcinia gummi-gutta
	Metformin	Grifola frondosa
		L-tryptophan
Resveratrol	Quercetin	Magnesium
	Trametes versicolor	Mebendazole
	Berberine	Medium-chain triglycerides
		Melatonin
Silybum marianum	DHEA**	Selenium
	Doxycycline**	Ursolic acid

TABLE 2: Reported metabolic and transporter interaction potential of the nonprescribed agents taken by the patient

Note: Inhibition categories based on data from [8-17]; **Possible, minor inhibition

The patient's condition gradually improved, and he successfully passed a spontaneous breathing trial. He was extubated two days after intubation. However, despite extubation, he remained significantly encephalopathic. Continuous electroencephalography (EEG) demonstrated no seizures; antiepileptic medications were discontinued, and IV fluids were administered. His mental status slowly improved, becoming able to answer simple questions and intermittently follow commands, although he remained intermittently confused with episodes of inappropriate profanity.

He was transferred from the neurological ICU to the general medicine service in stable condition one day after extubation. He was also started on quetiapine for delirium and agitation. The psychiatry service was consulted due to persistent encephalopathy and recommended discontinuing quetiapine in favor of haloperidol. The medical toxicology service was reconsulted due to his prolonged encephalopathy, which remained consistent with prolonged ivermectin toxicity in the setting of chronic use. A blood lead level was obtained and was normal.

Worsening confusion prompted repeat neurology service consultation. A repeat two-hour EEG was normal. Blood cultures subsequently grew *Escherichia coli*, with repeat cultures demonstrating clearance. Infectious disease service attributed the bacteremia to translocation of gut flora in the setting of recurrent colorectal malignancy. Surgical intervention was discussed with the patient, who was adamantly opposed.

His hospital course was complicated by ventilator-associated pneumonia with methicillin-sensitive *Staphylococcus aureus* (MSSA), gout exacerbation, and anemia of chronic disease requiring transfusion; these issues were managed appropriately and resolved before discharge. While his encephalopathy may have been worsened by these infectious findings, the encephalopathy notably preceded infection and lasted well after clearance of the infection.

Given his high risk for recurrent bacteremia and infectious complications, he was discharged to a rehabilitation hospital with continued IV antibiotics; a tapering regimen for haloperidol, clonazepam, and valproic acid; and outpatient follow-up with colorectal surgery and oncology services. He was also instructed to discontinue ivermectin and all non-prescribed supplements.

At the time of discharge, he was alert and oriented to person, place, time, and situation with intact repetition, fluency, and comprehension. Immediate recall and five-minute delayed recall were 3/3. Functionally, he required moderate assistance with activities of daily living, including dressing, and minimal assistance with ambulation and transfers. He participated in physical therapy, occupational therapy, and speech-language therapy and was discharged home from inpatient rehabilitation one week later (Figure *1*). He achieved complete resolution of encephalopathy and returned to baseline functional status; however, he continued to decline surgical management of his colorectal malignancy and was subsequently lost to follow-up after traveling abroad.

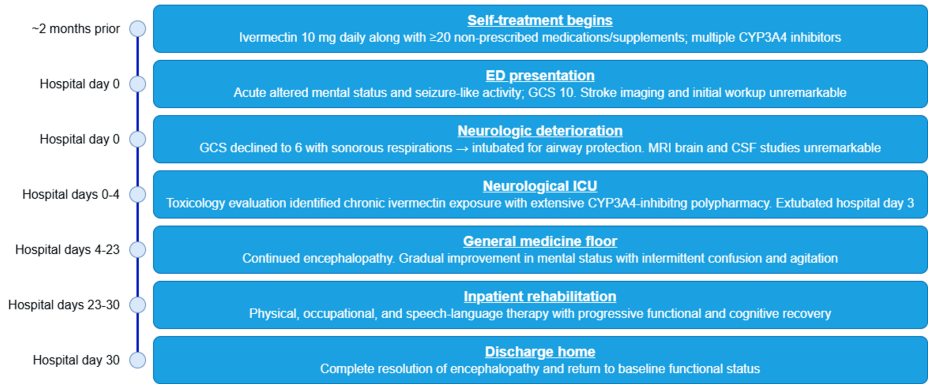


FIGURE 1: Clinical course timeline

Discussion

Published cases of ivermectin toxicity have most commonly involved supratherapeutic exposure, veterinary formulations, or prolonged off-label use. In a retrospective series of 37 cases, chronic users generally ingested lower daily doses over several weeks and developed milder toxicity than patients with acute exposures [2]. Severe neurotoxicity has also been reported after therapeutic-range dosing in susceptible individuals, including a patient with loss-of-function *ABCB1* mutations, the gene that encodes for P-glycoprotein [18]. More recently, cases of ivermectin-associated neurotoxicity have been reported in patients using supratherapeutic doses of ivermectin for self-directed treatment of COVID-19 [2] or malignancy [19]. Our patient represents a distinct presentation in which severe, prolonged neurotoxicity correlated with self-directed treatment of malignancy using ivermectin with long-term daily dosing, in the setting of potential CYP3A4-inhibiting polypharmacy.

Ivermectin exerts its antiparasitic activity through activation of glutamate-gated chloride channels in invertebrates, resulting in paralysis and death. In mammals, CNS exposure is generally limited by the blood-brain barrier, in part through P-glycoprotein, an ATP-dependent efflux transporter that restricts ivermectin penetration into the CNS [3,4]. Following oral administration, ivermectin undergoes hepatic metabolism predominantly through CYP3A4, with minor contributions from CYP3A5 and CYP2C9 [3]. Its reported elimination half-life is approximately 18 hours, although pharmacokinetic characteristics may vary with the population and formulation [3,4]. Daily administration over approximately two months, as reported in this case, could therefore have resulted in sustained exposure compared with the short-course regimens typically used for antiparasitic treatment.

Several agents in the patient's regimen have been reported to inhibit CYP3A4, although the magnitude and clinical relevance of these interactions in this patient are uncertain [8-17]. The extent to which these agents altered ivermectin metabolism or whether P-glycoprotein function was impaired cannot be determined. Nevertheless, chronic ivermectin exposure in the setting of extensive polypharmacy provides a plausible mechanism for altered drug disposition and enhanced neurotoxicity. At sufficiently high concentrations, ivermectin may affect mammalian inhibitory neurotransmission, including gamma-aminobutyric acid (GABA)-gated chloride channels, and has been associated with neurological manifestations ranging from ataxia, confusion, and somnolence to seizures, coma, and respiratory depression [2-4]. The patient's profound encephalopathy, seizure-like activity, and prolonged recovery, despite unrevealing neuroimaging and CSF studies, are compatible with severe ivermectin-associated neurotoxicity, although a causal relationship cannot be definitively established.

We propose that the patient's prolonged encephalopathy resulted from (i) chronic ivermectin exposure; (ii) concurrent administration of multiple CYP3A4 inhibitors leading to reduced hepatic clearance; and (ii) potential impairment of P-glycoprotein-mediated efflux, resulting in sustained CNS accumulation and neurotoxicity.

Of the 21 supplements and non-prescribed medications that the patient was taking for alternative cancer treatment, 10 of these may have contributed to his presentation (Table *2*). Cimetidine, resveratrol, and Silybum marianum are known inhibitors of CYP3A4 as well as CYP2C9 [8-10]. Artemisia, berberine, metformin, quercetin, and *Trametes versicolor* are known inhibitors of CYP3A4 [11-15]. There is some evidence that both dehydroepiandrosterone (DHEA) and doxycycline are possible inhibitors of CYP3A4, though this effect is minor if at all [16,17]. The simultaneous administration of numerous CYP3A4 inhibitors raises concern for additive impairment of ivermectin clearance [3,8-17]. This cumulative pharmacokinetic burden may have impaired ivermectin clearance and contributed to sustained exposure, providing a plausible explanation for the patient's unusually prolonged encephalopathy (Figure *2*). Although the patient was not taking overtly supratherapeutic doses of ivermectin, he was taking ivermectin daily for significantly

longer than the typical three-day regimens for parasitic infections [1], allowing for supratherapeutic blood levels of the drug.

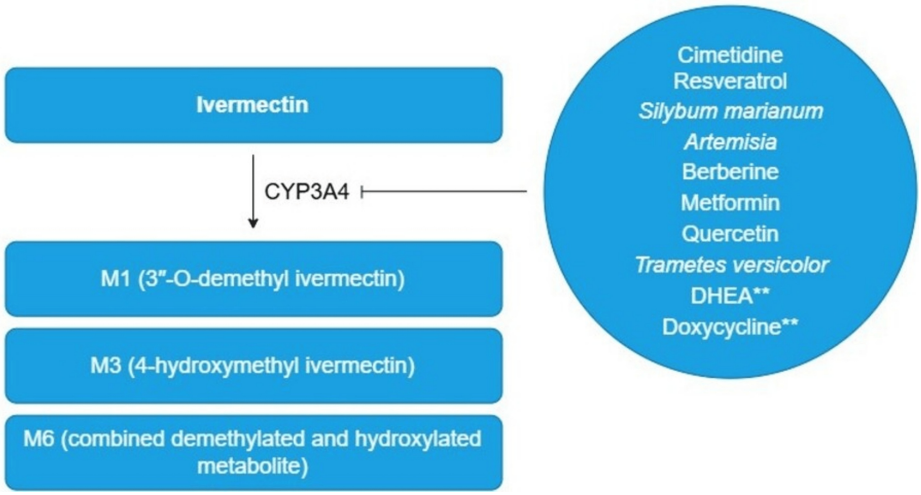


FIGURE 2: Ivermectin CYP3A4 metabolism

Proposed inhibition of CYP3A4 by co-ingested substances, allowing for chronic ivermectin toxicity.

Image credits: R. Blackmer; created using Draw.IO (https://app.diagrams.net/)

The patient's medication regimen reflects a broader trend of individuals pursuing alternative therapies for cancer treatment. Ivermectin has attracted considerable attention because of preclinical studies demonstrating potential antitumor activity through induction of apoptosis, disruption of Wnt/β-catenin signaling, inhibition of PI3K/Akt/mTOR pathways, and modulation of mitochondrial function. While these findings may seem promising, nearly all supporting evidence is limited to cell culture and animal models [5-7]. To date, no high-quality clinical trials have demonstrated meaningful therapeutic benefit of ivermectin in patients with malignancy, and professional oncology organizations do not recommend its use outside of clinical research [5]. Regardless, social media platforms, online discussion forums, and alternative medicine websites continue to promote ivermectin, often alongside complex supplement regimens marketed as synergistic anticancer therapies. This case illustrates how patients may unknowingly expose themselves to significant toxic risk while attempting to pursue unproven therapies.

Several important clinical lessons emerge from this case. First, comprehensive medication reconciliation should extend beyond prescribed medications to include supplements, herbal products, and medications obtained through a means other than prescription. Patients may not consider these products to be "medications" and therefore may not voluntarily disclose their use unless specifically asked. Second, unexplained encephalopathy with unremarkable neuroimaging, CSF analysis, and EEG should prompt consideration of toxic causes, especially when collateral history reveals use of alternative medical therapies. Early involvement of medical toxicology services can assist with identification of potential drug interactions, supportive management, and prognostication. Finally, this case highlights the importance of considering pharmacokinetic interactions rather than focusing solely on the toxicity of an individual medication. Even agents with relatively favorable safety profiles may produce severe adverse effects when combined with medications or supplements that alter their metabolism. Because of this, clinicians should proactively counsel oncology patients about the risks of unregulated internet-sourced therapies and document such counseling in the medical record.

The suspected adverse drug reaction was assessed as possibly related to ivermectin exposure, with chronic daily administration and concurrent use of multiple agents with reported CYP3A4 inhibitory potential providing a plausible pharmacokinetic explanation. However, causality cannot be established definitively because serum ivermectin concentrations and pharmacokinetic assessments were unavailable, the clinical relevance of the proposed drug interactions remains uncertain, and alternative contributors to encephalopathy could not be completely excluded. The reaction was severe, given the profound encephalopathy, seizure-like activity, and need for endotracheal intubation for airway protection, followed by a prolonged recovery requiring inpatient rehabilitation. It was also serious by standard pharmacovigilance criteria because it resulted in hospitalization and was associated with a life-threatening clinical presentation requiring intensive care. This case highlights the potential for serious neurological adverse reactions during prolonged ivermectin use, particularly in the setting of complex, nonprescribed medication regimens, while underscoring the uncertainty inherent in attributing toxicity to a specific drug or pharmacokinetic interaction.

Several limitations constrain the interpretation of this case. First, serum ivermectin concentrations could not be measured despite consultation with a specialty reference laboratory, precluding confirmation of supratherapeutic systemic exposure. CYP3A4 activity and ivermectin pharmacokinetics were not assessed, and P-glycoprotein function or *ABCB1* genotype was not evaluated; therefore, the proposed contributions of altered hepatic metabolism and impaired CNS efflux remain hypothetical. Although several agents in the patient's self-directed treatment regimen have been reported to inhibit CYP3A4, the extent to which these interactions were clinically significant, individually or collectively, is uncertain. Routine toxicology testing was also limited in scope and cannot exclude exposure to substances not detected by the assays performed. Furthermore, multiple CNS-active medications were administered during hospitalization, including lorazepam, levetiracetam, quetiapine, haloperidol, clonazepam, and valproic acid, which may have influenced the patient's mental status or complicated assessment of the duration and severity of the encephalopathy. Infectious complications, including *E. coli* bacteremia and ventilator-associated pneumonia, may also have contributed to or prolonged encephalopathy, although the initial neurological deterioration preceded their recognition and encephalopathy persisted beyond their resolution. Taken together, the exposure history, clinical presentation, and exclusion of several alternative etiologies support ivermectin-associated toxic encephalopathy as a leading diagnostic consideration. However, the absence of confirmatory drug concentrations and pharmacokinetic or transporter assessments, together with potential medication-related and infectious confounders, prevents definitive attribution of the clinical course to ivermectin toxicity or to CYP3A4/P-glycoprotein-mediated interactions.

Conclusions

This case demonstrates severe, prolonged encephalopathy associated with ivermectin toxicity in a patient self-treating colorectal cancer using ivermectin and numerous non-prescribed medications and supplements. Many of these medications inhibit CYP3A4, with extensive polypharmacy likely increasing systemic ivermectin exposure and contributing to prolonged encephalopathy.

As the use of alternative cancer therapies and internet-sourced medications continues to increase, clinicians should maintain a high index of suspicion for drug toxicity and clinically significant drug-drug interactions. For emergency and critical care clinicians, this case reinforces that unexplained encephalopathy with negative neuroimaging should prompt targeted history-taking for alternative therapies and potential CYP3A4/P-glycoprotein-mediated interactions.

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.

Acquisition, analysis, or interpretation of data: Hunter T. Pham, Ryan Blackmer, Bryan Judge, Maxwell Olson, Cody Stewart

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Supervision: Hunter T. Pham, Bryan Judge

Concept and design: Ryan Blackmer, Bryan Judge

Drafting of the manuscript: Ryan Blackmer

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Corewell Health Institutional Review Board issued approval CHRI-3950. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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