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Case Report

Transient Coma and Signs of Encephalopathy Related to 5-Fluorouracil and Carboplatin: A Case Report

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Abstract
Chemotherapy-related encephalopathy is a rare but severe side effect of cancer therapy. Few reports exist on the course of encephalopathy due to 5-fluorouracil (5FU)/carboplatin treatment. Here, we report on a patient in his 70s, who received first-line palliative treatment with carboplatin followed by continuous infusion of 5FU against a metastasized cancer of the base of the tongue. During the first 5FU infusion, the patient developed a coma with sudden onset. In contrast to earlier reports of 5FU-induced encephalopathy, serum ammonium levels were near-normal, despite a slightly increased bilirubin. The electroencephalogram showed signs of general encephalopathy, for which no other probable cause than chemotherapy could be identified. Based on historical reports, the patient's encephalopathy was likely due to 5FU treatment rather than carboplatin. While initially in a coma with a Glasgow Coma Scale score of three, the patient regained consciousness within 3 days of supportive therapy. This case highlights the potentially benign clinical course of 5FU-induced encephalopathy, characterized by fulminant clinical deterioration and quick recovery. Such a rapid deterioration in a palliative setting can pose a clinical dilemma, where invasive treatments such as intubation must be weighed against a limited prognosis, for which this case may provide guidance.

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Introduction

Encephalopathies are rare side effects of chemotherapeutics. Important oncological drugs that can cause encephalopathy are ifosfamide [1] and methotrexate [2]. Although carboplatin-related encephalopathy has been described in at least 1 patient [3], a systematic analysis of electroencephalogram (EEG) patterns before and after chemotherapy with carboplatin and paclitaxel did not reveal any signs of therapy-induced cerebral alterations [4].

5-Fluorouracil (5FU) is one of the most widely used chemotherapeutic drugs [5]. 5FU is a fluoropyrimidine that interferes with the metabolism of both DNA and RNA at different levels [6]. The safety profiles of fluoropyrimidines are well-described; clinically significant and often dose-limiting side effects (grade 3 or higher according to the Common Terminology Criteria for Adverse Events [CTCAE]) occur in more than 20% of all patients and are mainly dose-dependent [5]. The most common side effects include diarrhea, neutropenia, and hand-foot syndrome [6], while cardiotoxicity occurs less frequently but is potentially lethal [7]. Case reports and historical case series have described patients with central neurotoxicity after or during 5FU treatment. As early as the 1960s, cerebellar toxicity upon 5FU administration was reported [8]. Thirty years later, a case series of 7 patients with encephalopathy related to continuous 5FU infusion was published [9], all of whom had highly elevated serum ammonium levels.

Here, we present a case of 5FU-induced coma and encephalopathy characterized by near-normal ammonium levels, rapid clinical deterioration, and recovery within 3 days of supportive treatment. This case stresses that intensive care might be motivated even in palliative situations, for this complication because of its transient nature. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531472).

Case Presentation

A retired hairdresser in his mid-70s was referred to Karolinska University Hospital because of weight loss and thoracal discomfort. He had been an intermittent smoker and consumed alcohol moderately. His medical history included Langerhans cell histiocytosis of the central nervous system, diagnosed in the 1970s, secondary pituitary insufficiency with impaired antidiuretic hormone and gonadotropin axes, and he had previously been treated with transurethral resection of the prostate for benign hyperplasia. He was vaccinated three times against SARS-CoV-2 several months before the cancer diagnosis, and he was in good performance status (Eastern Cooperative Oncology Group [ECOG], 0–1).

CT and complementary PET-CT scans revealed multiple noduli in all lung lobes. Ventral of the left carotid artery, a multicystic tumor of 35 × 35 × 31 mm was seen, together with suspected ipsilateral cervical lymph node metastases. The radiology of the abdomen was unremarkable. A biopsy of the oral mass from the base of the tongue showed partial infiltration of microcystic to solid basaloid cancer with variable Ki67 expression in 10–50% of the tumor cells. No mutations in *EGFR*, *KRAS*, *NRAS*, *BRAF,* or *PIK3CA* were found. Human papillomavirus DNA qPCR and p16 immunhistochemistry were negative. Immunohistochemistry for PD-L1 (clone SP263) was negative (the tumor proportion score [TPS] was <1% and the combined positive score [CPS] was <1). In light of inconclusive findings despite extensive workup and pending additional pathological evaluation, the multidisciplinary tumor board suggested first-line palliative treatment with a doublet of carboplatin and 5FU, followed by radiotherapy of the oral primary tumor for local control. After

the palliative treatment had started, next-generation sequencing (NGS) revealed rearrangement of *MYBL1,* resulting in the diagnosis of high-grade adenoid cystic carcinoma with predominant solid growth pattern.

The dihydropyrimidine dehydrogenase testing (*DPYD* genotype) was normal, indicating a normal 5FU metabolism. The treatment with carboplatin was administrated at an area under the curve of 5 (Calvert formula), corresponding to 440 mg; the 5FU dose was 1,000 mg/m^2 per day in 5 days via a continuous i.v. infusion. The cumulative 5FU dose was 8,800 mg (1,760 mg/24 h). Premedication included 8 mg of betamethasone and 8 mg of ondansetron on the first two days of the cycle.

On the third day, under ongoing 5FU infusion, the patient presented to the emergency department with nausea, vomiting, loss of appetite, and general weakness. Diarrhea, pain, or any focal infection symptoms were absent. The vital signs were normal, and the patient was afebrile. The initial blood work results showed mild leukocytosis with a white blood count of 9.8 × 10^{E9}/L (normal: 3.5–8.8), neutrophils 8.1 × 10^{E9}/L (1.6–5.9), hemoglobin 154 g/L (134–170), platelet count of 228 × 10^{E9}/L (145–348)), Na+ 140 mmol/L (137–145), K+ 4.8 mmol/L (3.5–4.6), creatinine 106 μmol/L (<100), bilirubin 32 μmol/L (<26), and lactate 2.7 mmol/L (<2.2). The nasopharynx SARS-CoV-2 RNA test was positive, with a Ct value of 36.7. The SARS-CoV-2 antibody test had a spike >250 U/mL (positive), and SARS-CoV-2 RNA in plasma was negative. Another nasopharynx SARS-CoV-2 RNA test was performed three days later, which was negative.

The patient was admitted for rehydration and received metoclopramide (10 mg × 3) and betamethasone (4 mg) for continuous nausea. Figure 1 illustrates the most central laboratory results and key therapeutic interventions from the day of admission.

On the evening of day two, the patient presented with accelerated vomiting, worsening tiredness, and mild disorientation. In the morning, the patient was found unresponsive with a Glasgow Coma Scale (GCS) of three, isochore pupils, reactive to light, and absent reaction to pain. Acute CT angiography of the brain showed no sign of stroke; the basilary artery and the intracerebral arteries had normal flow, and no sign of bleeding was noted. A follow-up CT on the evening of the same day did not reveal any changes and excluded sinus vein thrombosis. The patient was transferred to the intermediary intensive care unit and received 3 g of levetiracetam without overt clinical improvement. The EEG the same night showed signs of slowed background activity and abundant triphasic waves, suggestive of encephalopathy. A lumbar puncture was performed, showing an opening pressure of 11 cmH_2O. Cerebrospinal fluid (CSF) analysis yielded clear liquid, and 1 × 10^{E6} /L leukocyte (normal: 0–5), 123 × 10^{E6}/L red blood cells (normal: <1), lactate 3.5 mmol/L (normal: 1.1–2.4), glucose 6.6 mmol/L, CSF/plasma glucose ratio of 0.57. CSF albumin 191 mg/L (normal: <9.0), and CSF/serum albumin ratio 5.0 E × 3 (normal: <9.0). Neuronal antibody screening (IFL) was negative, neurofilament light protein 660 ng/L (normal <1,850). Enterovirus RNA, HSV1 DNA, HSV2 DNA, and varicella DNA were negative in the CSF. A point-of-care cardiac ultrasound was normal. Serum ammonium levels were 35 μmol/L on day three and 30 μmol/L on day four (normal range: 11–32 μmol/L).

A magnetic resonance imaging (MRI) was planned but not performed due to clinical improvement toward the afternoon of day three. On the evening of day three, the patient started moving his arms and rolled over in the hospital bed. On the morning of day four, the patient opened his eyes, could leave the bed with the help of one person, and engaged in basic communication but was not oriented to time and space.

A blood culture taken on day two showed significant growth of *Staphylococcus saccharolyticus* after 110 h of culture. A urine bacterial culture yielded *Escherichia coli* (>E5). Another blood culture on day four showed growth of *Staphylococcus epidermidis* after 22 h of

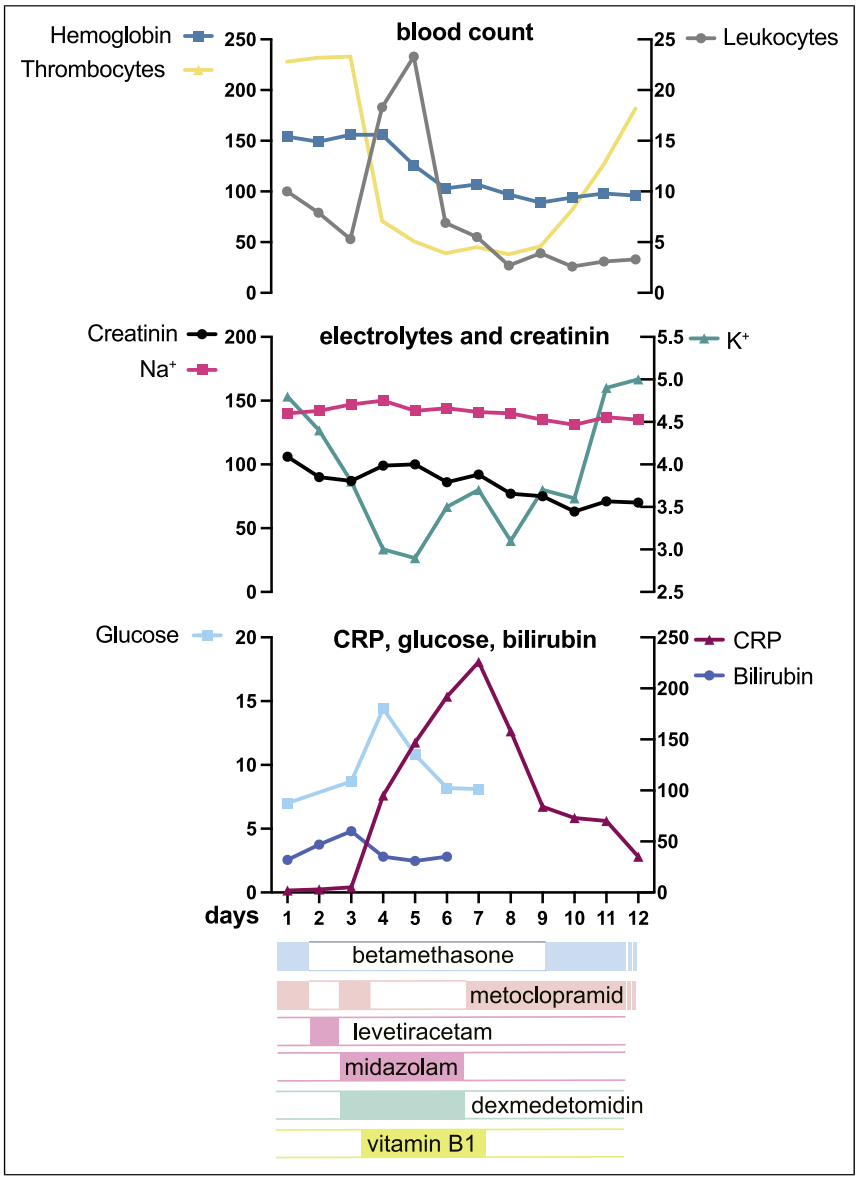

Fig. 1. Laboratory findings and treatment of a patient with 5FU-related encephalopathy. Laboratory results are shown per day when available, day 1 was the day of admission, and signs of encephalitis became overt on the evening of day 2. Reference values are CRP: <3 mg/L, leukocytes: 3.5–8.8 × 10^{E9}/L, hemoglobin: 134–170 g/L, thrombocytes: 145–348 × 10^{E9}/L, creatinine: <100 µmol/L, Na+: 137–145 mmol/L, K+: 3.5–4.6 mmol/L, bilirubin: <26 µmol/L, glucose: 4.2–6.0 mmol/L. The colored bars below the *x*-axis represent the days on which a given drug was administered. The list of administered drugs is limited to those potentially affecting the central nervous system. Antibiotic treatment is described in the text. In addition, the patient received crystalloid infusions not listed here.

culture, while other blood cultures on days three, four, and five remained negative. On day three, the patient was started on cefotaxime for a suspected urinary tract infection at a time, when vigilance levels had already increased. He was transferred back to the oncology ward and continuously improved during the coming week, after which he was discharged. One month after the episode, he was seen in the outpatient clinic and had a performance status of 0–1 (ECOG), regularly undertaking daily, hour-long walks.

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Discussion

We here report a patient who developed a coma with signs of encephalopathy during infusion of 5FU. Our patient's clinical course is similar to those of 7 patients described previously [9]; these patients with different primary tumor sites had received continuous 5FU over 3 to 5 days; two of them had liver metastases. All 7 patients developed a coma with rapid onset during or shortly after the 5FU infusion. In contrast to our patient, all those patients had highly elevated plasma ammonium levels. Six of the 7 patients quickly recovered from coma under supportive therapy [9]. The patient described in our report had near-normal serum ammonium levels while in coma, suggesting hyperammonemia as an unlikely cause for the fulminant neurological impairment. Five of the patients in the previous case series had concomitant infections [9]; also in our case, fever, elevated CRP, and a positive blood culture suggest systemic infection. However, this occurred after the onset of neurological impairment, suggesting that infection was an unlikely trigger.

Also in a larger series of 32 patients with hyperammonemic encephalopathy related to 5FU infusion, infection was commonly seen [10]. Interestingly, the authors found that in patients without infection, encephalopathy was related to dehydration [10]. Our patient was admitted with nausea and vomiting (possibly related to carboplatin), and in the two subsequent days after admission, elevated levels of hemoglobin and creatinine were noted, suggesting hypovolemia. A retrospective chart review revealed that on days one and two after admission, the patient had not taken the antidiuretic desmopressin, which he had been prescribed for antidiuretic hormone deficiency. This observation could point to dehydration significantly aggravating 5FU toxicity. In another report of 2 patients with transient 5FU-related encephalopathy [11], the authors discussed that impaired urea metabolism, for example, by kidney dysfunction, might increase ammonium levels and thereby could lead to encephalopathy. In addition, the toxic 5FU metabolite, fluoroacetate might directly inhibit the urea cycle [12, 13]. Given the near-normal ammonium levels in the patient presented here, it is possible that dehydration might have increased 5FU plasma concentration, causing encephalopathy by direct toxicity. We found one report of a similar patient case with normal ammonium levels [14]; in addition, a survey of French pharmacovigilance data from 1986 to 2018 has identified 2 patients with signs of encephalopathy but without hyperammonemia after 5FU treatment, while 30 patients with elevated ammonium levels and encephalopathy were identified in the same time frame [15]. These data suggest that 5FU-related encephalopathy with normal ammonium levels is extremely rare. However, we did not find any data on serum levels of 5FU and encephalopathies with normal serum levels, which could have strengthened the hypothesis of direct toxicity in the case of high 5FU levels.

Of note, 5FU-induced central neurotoxicity can present in various forms such as Wernicke encephalopathy [16], mimic stroke [17], or cause progressive dementia [18], suggesting both metabolic and direct 5FU toxicity as a possible mechanism. Some studies have reported the successful treatment of 5FU-related encephalopathies with the 5FU antagonist, uridine triacetate [19, 20], which might be a therapeutic option for 5FU-associated acute central nervous system toxicities with and without elevated ammonium levels, but which is not yet broadly available [21]. Encephalopathies have also been reported during treatment with the 5FU prodrug, capecitabine, implying that a switch to capecitabine might not be a safer alternative [22–24].

Finally, posterior reversible encephalopathy syndrome (PRES) has been associated with 5FU treatment [25], although it is more commonly related to immunosuppression, the monoclonal antibody bevacizumab [26], or other chemotherapeutics [27]. PRES is a syndrome that includes altered mental status, visual disturbances, headache, and seizures [27]. MRI is required for a definitive diagnosis. In the case of our patient, no MRI was done because of rapid improvement. Nevertheless, the clinical presentation of our case excludes PRES, and the EEG findings are suggestive of general encephalopathy.

Conclusions

Our case highlights the potentially transient nature of central, 5FU-related neurotoxicity, irrespective of an association with hyperammonemia, and underscores that treating dehydration and infection might facilitate recovery.

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Statement of Ethics

Publication of the patient data in this case report did not require approval by the Local Ethical Committee, according to Swedish legislation, SOU 2017:104, and SFS 2003:460 (changed SFS 2018:1999) "*Lag om etikprövning av forskning som avser människor*." Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The authors declare that no competing interests exist.

Conflict of Interest Statement

The authors declare that no conflicts of interest exist.

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Author Contributions

M.G. and M.Z. wrote the manuscript and gathered the clinical data. T.E.C. and K.K.A. contributed to the conception and critical revision of the manuscript. M.G., T.E.C., and K.K.A. participated in the clinical treatment. S.F. and P.F.N.d.S. read and critically commented on the manuscript. All the authors approved the final version to be published and agreed to act as guarantors of the work.

Data Availability Statement

All data gathered for this case report are included in this article. Further inquiries can be directed to the corresponding author (M.G.).

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