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5 FU-Induced Encephalopathy: A Rare Side Effect with Many Variants. A Case Report of a Patient with Colorectal Cancer and Non Hyperammonemic Fluorouracil Induced Encephalopathy

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Abstract

Introduction: One of the first chemotherapeutic drugs reported to exert anticancer activity 5-Fluorouracil (5-FU) has been considered for many years as the mainstay of many chemotherapy regimens for a variety of malignant tumors. Most commonly recorded side effects are myelosuppression, gastrointestinal disorders, mucositis, hand–foot syndrome and rarely cardiac toxicity. More rarely, 5-FU infusion can induce neurologic abnormalities such as cerebellar ataxia and changes in cognitive function.

Case presentation: Herein, we present the case of a patient diagnosed with colorectal cancer presenting acute neurologic adverse effects related to fluorouracil administration. Although increased serum ammonia levels were not recorded, distinct leukoencephalopathy signs were noted in the brain MRI. Despite the lack of specific clinical guidelines regarding the management of 5-FU induced encephalopathy, intravenous hydration plus thiamine supplementation and laxatives were administered. Five days following the onset of the symptoms the patient started showing signs of improvement.

Conclusion: Clinicians need to be aware of the adverse neurologic effects of fluorouracil and include them in the differential diagnosis, when patients receiving the drug present with neurologic symptoms, in order to ensure prompt diagnosis and effective treatment. Furthermore, genetic DPYD screening is also recommended prior to administration of fluorouracil-based regimens.

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Introduction

One of the first chemotherapeutic drugs reported to exert anticancer activity 5-Fluorouracil (5-FU) has been accepted for many years as the mainstay of many chemotherapy regimens for various tumor types. In 1962 FDA approved the use of this anti-metabolite agent for the treatment of Colorectal Cancer (CRC) and since its first approval, 5-FU has been widely used either alone or in combination with other drugs to treat different malignant tumors including colorectal, anal, pancreatic, gastric, esophageal, breast, skin as well as head and neck cancers [1]. Most commonly recorded side effects are myelosuppression, gastrointestinal disorders, mucositis, hand–foot syndrome and rarely cardiac toxicity [2]. Although uncommon as a phenomenon 5-FU infusion can induce neurologic abnormalities such as cerebellar ataxia and changes in cognitive function and a few cases are reported [3].

Case Presentation

In May 2023 a 73 year old male presented with anemia and within a month began experiencing symptoms of progressively increasing generalized weakness, fatigue, and hematochezia. He had been an intermittent smoker (30 py) without a history of alcohol consumption. His medical history included benign hyperplasia of the prostate, arterial hypertension and retroperitoneal fibrosis. He underwent a colonoscopy revealing a hard circular polypoid mass, on the right colic flexure, which was causing narrowing of the lumen and did not allow for further advancement of the scope. Biopsies were collected and pathology results confirmed the diagnosis of right-sided ascending colon adenocarcinoma. The patient was presented with excessive bleeding and underwent an urgent right hemicolectomy in June 2023. A low grade adenocarcinoma NOS, pT3 N1a M1a was detected, invading through the muscularis propria into pericolorectal tissues, one regional lymph node was found to be positive (Lns1^{+}/15) and hepatic metastasis was identified. Following surgery, the patient underwent CT scans of the thorax and abdomen which revealed multiple hepatic metastases. The Dihydropyrimidine Dehydrogenase testing (DPYD genotype) was normal, indicating a normal 5FU metabolism, the test for mutations in NRAS was negative while KRAS G12V mutation was revealed. About 7 weeks post-surgery, he was admitted to receive his first cycle of FOLFOX chemotherapy, which consisted of Oxaliplatin 85mg/m^2 (total dose of 110 mg), Leucovorin 400 mg/ m^2 (total dose of 530 mg), 5 FU bolus 400mg/m^2 (total dose 530 mg) and 5FU 1200 mg/m^2/24h (1550mg/24h) via a continuous i.v. infusion. The cumulative 5FU dose was 3100 mg (1550 mg/24 h) and premedication was administered according to guidelines. Total dose of the chemotherapy regimen was decreased by 20% due to the general performance status of the patient (Eastern Cooperative Oncology Group [ECOG], 1). On the first day of chemotherapy, he had no specific complaint. During the end of the 2nd day of chemotherapy the patient complained of epigastric pain solely with no other symptoms. The intravenous administration of 5 FU was immediately discontinued and ECG was performed without any recorded pathological clinical finding. Vital signs did not reveal any abnormalities. Due to deterioration of his communication level a neurological assessment was requested, and the CT of the brain which was consequently performed (with intravenous contrast) found to be negative for any abnormalities. Blood biochemistry and arterial blood gas analysis did not initially reveal irregular values. Within hours intense agitation was observed and the patient complained of severe headache with epigastric pain. Measured oxygen and carbon dioxide levels in the arterial blood gas analysis were normal, lactate was elevated (2.6 mmol/L) without acidemia (pH 7.52, bicarbonate 21 mmol/L). Furthermore, intravenous hydration started as serum urea and creatine levels were recorded elevated with hyperphosphatemia. In the neurological examination a cognitive decline was reported and he was diagnosed with a Glasgow Coma score of 10 on a scale of 15, with the following elements:

- Verbal response 3 of 5 (inappropriate words)
- Eye opening 3 of 4 (eye opening to verbal command)
- Motor response 4 of 6 (withdraws from pain).

Large volume hydration was maintained along with the addition of thiamine due to further increased levels of lactate and phosphate in conjunction to serum urea and creatinine values. Additionally, laxatives administration was further initialized. Serum ammonia measured level in peripheral blood sample, tested in external laboratory three days following the onset of patient's symptoms, revealed within normal range (31μg/dL). Electrical activity with electroencephalography test showed basic (α) rhythm and occasional (θ) waves in the frontal and central lobe with mild right hemisphere predominance and without any epileptiform patterns. Diffusion-weighted brain Magnetic Resonance Imaging (MRI) showed high-intensity areas in the periventricular white matter and corpus callosum. Subsequently, with 4 days of intravenous hydration plus thiamine supplementation and laxatives administration, patient started showing signs of improvement. All the laboratory findings were improved to be within normal range and the patient's mental status also completely recovered. The fluctuations in the arterial blood gas analysis markers from the onset until the improvement of the symptoms of the patient are presented in **Table 1**. Patient was then discharged after 10 days of hospitalization in a good clinical condition. He was re-admitted again after a month to continue the chemotherapy although the regimen was now changed to Irinotecan (180 mg/m^2 reducedby 20% with a total dose of 230 mg every 14 days). Symptoms were monitored closely, and he was finally discharged without any side effects. He is presently receiving Irinotecan and no additional adverse events have been recognized until today.

Table 1: Describing the fluctuations in the arterial blood gas analysis markers daily from the onset until the improvement of the symptoms of the patient.

ABG	Day 1	Day 2 (morning)	Day 2 (evening)	Day 3	Day 4	Day 5
PH	7,50	7,65	7,38	7,47	7,46	7,44
PCO_2 (mmHg)	29	18	30	29	33	31
PO_2 (mmHg)	115	143	117	106	92	93
HCO_3- (mmol/L)	24	20	21	21,1	23,5	22,9
Lac (mmol/L)	0,8	2,6	6	3,3	2,7	1,1

ABG: Arterial Blood Gas; pCO_2: Partial pressure of carbon dioxide; pO_2: Partial pressure of oxygen; HCO_3: Bicarbonate; Lac: Lactic acid.

Discussion

To exert its cytotoxic effect, 5-FU has to reach the tumour site, enter into cells, and be phosphorylated into its three active metabolites (5-FdUMP, 5-FdUTP and 5-FUTP). With a half-life of less than 20 min, soon after its administration in patients, 5-FU is catabolized in the liver into pharmacologically inactive metabolites [4]. Dihydropyrimidine Dehydrogenase (DPD), is a crucial enzyme with a major role in the catabolism of 5-FU. The

possible existence of a relevant polymorphism in its gene has therefore been extensively studied for its role in the efficacy degree as well as for the toxicity of 5-FU [5]. There is now evidence that 5-U toxicities can be worsened by complete or partial genetic and/or phenotypic dihydropyrimidine dehydrogenase deficiency due to excessive accumulation of 5-FU in the body [6]. Hence nowadays, all institutions in Greece advice patients, candidates for fluorouracil-based therapy to have a DPYD test done before the onset of therapy. Normal Dihydro Pyrimidine Dehydrogenase testing (DPYD genotype) is indicative of a normal 5FU metabolism and therefore the patient will have a somehow safe clinical course. The most common clinical manifestations of 5-FU toxicity include among others:fever, fatigue, mucositis, stomatitis, nausea, diarrhea leukopenia, thrombocytopenia, anemia, neuropathy and skin rash[7]. Encephalopathy and neurologic abnormalities such as cerebellar ataxia and changes in cognitive function have also been rarely reported, occurring in <1% of the patients [8]. The 5-FU induced encephalopathy may present as either hyperammonemic encephalopathy, leukoencephalopathy, or Wernicke encephalopathy. As aggravating factors of 5-FU induced encephalopathy, renal dysfunction, azotemia, dehydration, constipation and bacterial infections are believed to contribute to its development [9]. The exact etiology remains uncertain although it is believed that two different mechanisms contribute to the development of 5-FU induced encephalopathy.The first presumed cause is Dihydropyrimidine Dehydrogenase (DPD) deficiency. As previously mentioned, in the case of DPD deficiency, 5-FU catabolism is considered poor, which later leads to excessive 5-FU accumulation within the body. Excess 5-FU levels can penetrate the blood-brain barrier and be detected in the cerebrospinal fluid causing in continue neurotoxic effects in the central nervous system, such as acute demyelination of neurons while has been demonstrated to may also increase the cellular thiamine metabolism leading to Wernicke encephalopathy [10,11]. The second pathophysiological mechanism involves one of the of 5-FU catabolites, the fluoroacetate which seems to directly inhibit Kreb's cycle, resulting in impairment of the ATP-dependent urea cycle. Thus, the conversion of ammonia to urea is prevented, leading to excess accumulation of ammonia. This mechanism is also considered as the causative pathway for the development of hyperlactatemia due to the facilitation in the lactic acid production [12]. No specific clinical guidelines exist regarding the management of 5-FU induced hyperammonemic encephalopathy. When suspected, the immediate discontinuation of 5-FU infusion is suggested as necessary, along with large volume hydration. Treatment with thiamine has also been recommended [13]. Diagnostic procedures including laboratory tests and imaging studies should be performed to rule out differential diagnosis. Although fatal outcomes have been reported, most patients with 5-FU induced hyperammonemic encephalopathy recover without complications, with the immediate discontinuation of 5-FU followed by supportive treatment including intravenous fluid hydration, thiamine and lactulose enema [14].

Conclusion

It is crucial for clinicians to be aware of the adverse neurologic effects of fluorouracil and include them in the differential diagnosis, when patients receiving the drug present with neurologic symptoms, in order to ensure prompt diagnosis and effective treatment. Genetic DPYD screening is also recommended prior to administration of fluorouracil-based regimens.

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