

Simultaneous Cardiotoxicity and Neurotoxicity Associated with 5-fluorouracil Containing Chemotherapy: A Case Report and Literature Review

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Abstract We present a case of simultaneous cardiotoxicity and stroke-like neurotoxicity in a patient treated with FOLFOX, a 5-Fluorouracil (5-FU)-containing chemotherapy regimen. Within hours of FOLFOX infusion, the patient began to exhibit signs and symptoms of myocardial ischemia and stroke mimic. Coronary vasoconstriction and vasospasm is a known mechanism of 5-FU-induced cardiotoxicity. 5-FU-induced neurotoxicity commonly presents as encephalopathy and is likely attributable to the accumulation of ammonia, a product of 5-FU metabolism. However, our patient presented with focal neurological signs and normal levels of ammonia. This suggests that 5-FU-induced vasospasm in the coronary arteries and cerebral vasculature is a likely cause of the simultaneous cardiac and neurological events we report here which have not been reported previously. Recognition of these toxicities as complications of 5-FU chemotherapy is crucial for the proper diagnosis and treatment of patients.

Keywords: FOLFOX, 5-fluorouracil, 5-FU, chemotherapy, cardiotoxicity, neurotoxicity

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1. Introduction

5-Fluorouracil (5-FU) is a cytotoxic chemotherapeutic agent, classified as an "antimetabolite," that is used in the treatment of different types of cancer including gastrointestinal malignancies. FOLFOX is a combination of chemotherapy drugs made up of 5-FU, oxaliplatin, and folinic acid. Common adverse effects of FOLFOX include increased risk of infection, bleeding, bruising, rash, nausea, vomiting, diarrhea, fatigue, and peripheral neuropathy [1]. Cardiac toxicity and stroke-like neurotoxicity are rare but reported severe adverse effects. We present here a case of simultaneous cardiotoxicity and stroke-like neurotoxicity in a patient treated with FOLFOX for stage IV gastric adenocarcinoma with metastases to the liver within a few hours of her first infusion.

2. Case Presentation

A 73-year-old female with a significant past medical history of gastric adenocarcinoma stage IV with liver metastasis (diagnosed two months earlier in October 2018), who presented to the emergency department (ED) with acute shortness of breath, difficulty swallowing, and

impaired speech. She received her infusion six hours before the onset of her symptoms, became short of breath, and had a choking sensation upon drinking water. She also noted facial droop and tingling in her fingertips, which prompted her to self-activate Emergency Medical Services. Other co-morbidities include hypertension and hypothyroidism. Upon arrival at the ED, she had expressive aphasia. She denied any motor deficits, headache, dizziness, or chest pain. On presentation, her vital signs were 97.9°F, heart rate 69 beats/min, respirations 18 breaths/min, and blood pressure 174/90 mmHg. Physical examination revealed right facial droop, with otherwise intact cranial nerves. Motor strength was 4/5 in bilateral upper and lower extremities, and the cardiac exam showed a regular rate and rhythm with no added sounds. Initial laboratory results showed leukocytosis 17.81 [3.50 - 10.80 K/uL], hyponatremia 130, [136 - 145 mmol/L], elevated creatinine 1.93, [0.70 - 1.30 mg/dL], blood urea nitrogen 43, [7 - 25 mg/dL], aspartate aminotransferase 317, [13 - 39 u/L], alanine transferase 68, [7 - 52 u/L], alkaline phosphatase 600, [34 - 104 U/L], initial troponin I 0.73, [??- <=0.15 ng/mL], which peaked to 3.63 ng/mL six-hour later. Initial EKG revealed normal sinus rhythm with septal Q waves and anterolateral T wave inversions (TWI). Repeat EKG (9 hours later) showed more prominent TWI in the septal leads. Transthoracic echocardiography showed wall motion

abnormalities in the anteroseptal wall and apex. CT head did not reveal acute stroke. CTA of the head was significant for moderate abnormal perfusion in the left middle cerebral artery (MCA) territory and stenosis at the bifurcation, but no large vessel occlusion was found. Oncology was consulted, and they recommended immediate discontinuation of the FOLFOX infusion. Neurology recommended aspirin, statin, permissive hypertension to 180s, and MRI/MRA. MRI/MRA done later during hospitalization showed narrowing of the left MCA, but no acute infarct of the brain. Neurological symptoms completely resolved within 24 hours after onset and were assumed to be due to FOLFOX treatment. Cardiology was consulted for EKG changes and elevated troponin and recommended treating as non-ST segment elevation myocardial infarction with anticoagulation and antiplatelet agents. Of note, the patient had an exercise stress echocardiogram one year earlier without any stress-induced wall motion abnormalities. The patient was planned for cardiac catheterization during the admission, which she later refused considering her overall prognosis after discussion with the palliative team.

3. Discussion

Cardiotoxicity is a rare but severe complication of 5-FU containing chemotherapies, occurring in 1-18% of patients receiving 5-FU [1] and with mortality in 2.2-13% of cases [2,3]. A frequent presentation of 5-FU induced cardiotoxicity is myocardial ischemia; however arrhythmias, hypertension, hypotension, left ventricular dysfunction, cardiac arrest, and sudden death have all been reported [3,4,5]. Cardiotoxicity due to 5-FU has yet to be defined and is likely multifactorial. However, one known mechanism is via coronary vasoconstriction and vasospasm, which lead to ischemic or non-ischemic cardiac events [1,5,6,7,8,9,10]. This theory is supported by visualization of vasospasm during coronary angiography [11,12], as well as by the short-lived nature of cardiac signs and symptoms and their rapid resolution upon administration of nitroglycerin and calcium channel blockers. Administration of these vasodilatory agents can lead to a complete cessation of chest pain and normalization of ECGs with the return to baseline [9]. The specific mechanism of 5-FU induced vasoconstriction and vasospasm likely includes the alteration of smooth muscle tone via molecular signaling pathways involving protein kinase C [1,5,10].

The schedule and dosing of 5-FU, as well as a patient's cardiac comorbidities, all appear to have a significant role in inducing cardiotoxicity. Patients receiving a continuous 5-FU infusion have a higher incidence of cardiotoxicity compared to those who receive a 5-FU bolus: 6.3% compared to 2.2% [3,13,14]. Similarly, increased rates of cardiotoxicity were found with a 5-FU + leucovorin or 5-FU + cisplatin infusions, compared to a 5-FU infusion alone [3,13]. Thus, both the scheduling of the therapy and the therapeutic adjuvants must be carefully considered when beginning treatment. Coronary artery disease (CAD) is a known risk factor for developing 5-FU induced cardiotoxicity [1,4]. Thus, patients with preexisting CAD should be considered for prophylactic nitroglycerin and calcium channel blocker therapy to prevent cardiac

complications. Pretreatment with glycerol trinitrate has been shown to avoid artery constriction upon initiation of a 5-FU containing chemotherapeutic treatment [9].

Neurotoxicity is another rare but potentially fatal adverse effect of 5-FU chemotherapies, occurring in 0.6-7% of patients receiving the chemotherapeutic agent [15,16,17]. 5-FU induced neurotoxicity commonly presents as encephalopathy, which sometimes can be mistaken for a stroke. Thus, reported cases in the literature have described it as a 'stroke mimic,' and clinical manifestations have included confusion, ataxia, dysmetria, nystagmus, focal weakness, generalized seizures and rarely, coma or death [18]. The mechanism of 5-FU neurotoxicity is not entirely understood, but likely pertains to the accumulation of ammonia, a product of 5-FU metabolism, or deficiency of dihydropyrimidine dehydrogenase, the rate-limiting enzyme of 5-FU catabolism [15,16,18]. The risk of hyperammonemia caused by 5-FU increases with comorbid conditions, including renal disease, infection, dehydration, and chronic constipation. These conditions are believed to cause increased ammonia production in the colon or increased reabsorption of urea from renal tubules [18,19,20]. Our patient, however, presented with focal neurological signs and her ammonia levels were within normal limits, suggesting the possibility of alternative pathophysiology. We recommend that 5-FU may induce vasoconstriction and vasospasm in the cerebral vasculature similar to the way it does in the coronary arteries. Although 5-FU has been associated with vascular endothelial damage, myocardial infarction and ischemic stroke [21,22], our patient's CT scan did not suggest ischemic stroke. Thus the likely etiology for simultaneous neuro and cardiac events in our patient is 5-FU induced vasospasm in the cerebral vasculature in addition to coronary vasospasm. Although the possibility of 5-FU induced coronary or cerebral plaque rupture should be considered in all cases of myocardial infarction or stroke, in our patient the events suggest simultaneous coronary and cerebral vasospasm.

Recognizing stroke mimics in patients on 5-FU chemotherapeutic agents such as FOLFOX is imperative for appropriate management. Importantly, 5-FU encephalopathy mimicking a stroke is not an indication for tissue Plasminogen Activator (tPA) administration [15], and when given, tPA can be associated with further complications. As neurological abnormalities in a patient with malignancy can be indicative of several scenarios, including brain metastasis, sepsis or metabolic abnormalities, neurotoxicity must be considered for patients undergoing chemotherapy with a 5-FU agent.

4. Conclusion

In summary, both cardiotoxicity and neurotoxicity are severe, but rare adverse effects of 5-FU-containing chemotherapeutic agents such as FOLFOX. To the best of our knowledge, ours is the first published case of a patient presenting with both cardiotoxicity and stroke mimic, possibly due to cerebral vasospasm, within six hours of the first dose of a 5-FU drug. With our patient, as with others, cessation of chemotherapy and symptomatic treatment resulted in the resolution of both the cardio- and neuro-toxicities. Recognition of these toxicities as

complications of 5-FU chemotherapy is crucial for the proper diagnosis and treatment of patients.

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