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Review Article

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ISCHEMIC STROKE SECONDARY TO INFUSIONAL 5-FLUORURACIL IN A PATIENT WITH RECTAL CANCER

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ABSTRACT

5-FU is antimetabolites that have been widely used in the treatment of various malignant diseases. A severe side effect to 5-FU based treatment is stroke-like neurotoxicity. ischemic stroke is rare but reported. there is no clear pathogenic explanation for these events, although a number of possibilities are put forward, including direct endothelium toxicity or arterial vasospasm. We present a case of stroke-like neurotoxicity in a patient with rectal cancer treated with FOLFIRINOX, a 5-Fluorouracil (5-FU)-containing chemotherapy regimen. The close temporal relationship between the end of 5-FU infusion and ischemic stroke points at chemotherapy as a reasonable cause suggest a causative relationship between chemotherapy and the ischaemic attack in this patient.Recognition of this toxicity as complications of 5-FU chemotherapy is crucial for the proper diagnosis and treatment of patients.

KEYWORDS: 5-Fluoruracil, rectal cancer, Ischaemic attack, Vascular toxicity.

INTRODUCTION

5-Fluorouracil (5-FU) is a chemotherapeutic agent extensively employed in the treatment of a wide range of solid malignant tumors, including colorectal cancer.[1] However, like other drugs used for chemotherapy, it affects the growth of normal body cells and often causes side effects such as hair loss, fatigue, birth defects, mouth sores and ulcers, liver disease, and a temporary drop in bone marrow function.[2,3]

Few cases of ischemic stroke after cancer treatment have been reported.[4] The causal relation between the perfusion of the antineoplastic agent and the thrombotic process is difficult to ascertain. Our aim in this study was to elucidate the risk of ischemic stroke after chemotherapy.

We report the case of a patient with rectal cancer who presented with an acute ischaemic attack, 3 days after initiation of the sixth cycle chemotherapy with 5-fluoruracil.

PATIENT REPORT

A 58-year-old female without vascular risk factors, diagnosed with rectal adenocarcinoma, for whom we opted for chemotherapy according to the protocol FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion) every 2 weeks.

3 days after initiating the sixth 5-FU infusion, the patient began to experience headaches, dizziness, impaired speech and motor deficits.

Neurological examination revealed a dysarthria and right hemiplegia. the cardiac exam showed a regular rate rhythm with no added sounds and blood pressure and pulse were normal.

Magnetic Resonance Imaging (MRI) of the Brain revealed a infarction area in the territory of the right medium cerebral artery and the left posterior cerebral artery (figure 1). An extensive study including electrocardiogram, transthoracic echocardiography, complete blood coagulation were normal . the ischemic event remained unexplained despite an extensive workup. The patient was diagnosed with an acute stroke-like event potentially caused by the 5-FU component of FOLFIRINOX therapy.

Neurologists have recommended anticoagulant therapy combining an antiplatelet agent and low molecular weight heparin.

The patient's condition rapidly deteriorated over a short period of time, she became somnolent, then comatose, she died 5 days later.

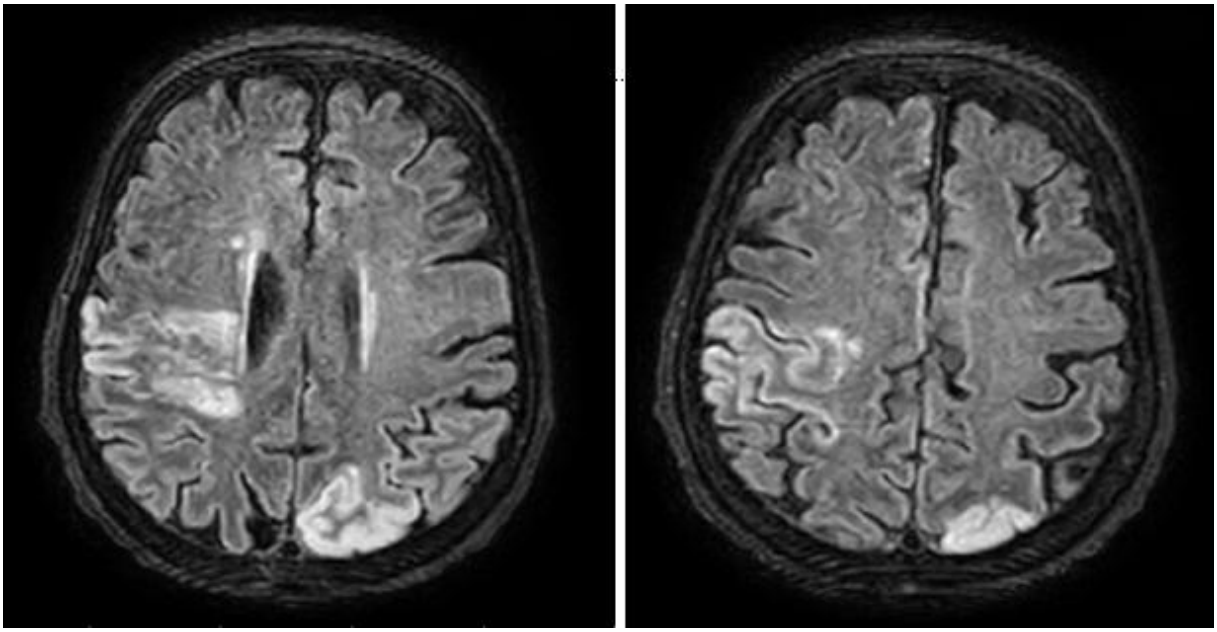

Figure 1: MRI showing a infarction area in the territory of the right medium cerebral artery and the left posterior cerebral artery.

DISSCUSSION

5-Fluorouracil (5-FU) is administered widely as a single agent or in multidrug regimens for various types of malignancies, including gastrointestinal, breast, and head and neck cancers.[5] Common side effects of 5-FU are bone marrow suppression leading to neutropenia and infections, and gastrointestinal toxicities such as stomatitis, nausea, vomiting, and diarrhea. Other less frequent adverse effects include alopecia, photosensitivity, and rarely, cardiotoxicity and neurologic toxicity.

Neurologic toxicity may manifest acutely as cerebellar syndrome as well as encephalopathy including cognitive impairment with somnolence, organic.

brain syndrome and dementia.[6] It may also manifest as a subacute multifocal leukoencephalopathy.[7]

Although ischemic stroke with fluorouracil is rare, they have been reported. The pathophysiological mechanism of this toxicity is still unclear, although several theories have been proposed including : direct endothelium toxicity, arterial vasospasm, or cooperation between the two mechanisms.

In an experimental study in rabbits, evaluating the immediate effect of 5-FU on vascular endothelium, severe damage to the ultima, occasionally followed by thrombus formation was seen.[8]

It has been shown that 5-FU causes coronary vasoconstriction and vasospasm, which lead to ischemic or non-ischemic cardiac events.[9,10,11,12,13,14,15] 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.[9,10,15] We recommend that 5-FU may induce vasoconstriction and vasospasm in the cerebral vasculature similar to the way it does in the coronary arteries.

Our patient was diagnosed with an ischemic stoke event caused by the 5-FU component of FOLFIRONOX therapy , because no other known cause could be found, the temporal relation between the end of 5-FU infusion and ischemic stroke and there are various studys published supporting the role of 5-FU in direct vascular and arterial vasospsm inducing thrombosis.

CONCLUSION

5-FU is an antineoplastic agent which has been connected with increased incidence of ischemic strokes.

Acute ischaemic cerebrovascular attack may be an underreported complication related to chemotherapy.

We must be aware of this potential complication in patients on 5-FU chemotherapeutic agents such as FOLFIRINOX for the proper diagnosis and treatment of patients.

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