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# POSSIBLE FRUQUINTINIB ASSOCIATED ISCHEMIC COLITIS IN A PATIENT WITH METASTATIC AMPULLARY ADENOCARCINOMA

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## ABSTRACT

*Introduction:* Ischemic colitis is a severe gastrointestinal condition resulting from compromised colonic perfusion and may occur as a rare adverse effect of anti-angiogenic therapies.

*Case description:* We report a case of severe acute ischemic colitis temporally associated with recent fruquintinib exposure, presenting with large-volume haematochezia in a patient with metastatic ampullary adenocarcinoma.

*Discussion:* Fruquintinib is a highly selective vascular endothelial growth factor receptor tyrosine kinase inhibitor approved for refractory gastrointestinal malignancies and is generally well tolerated. Although gastrointestinal toxicities are well described, ischemic colitis has not been well characterized in association with fruquintinib.

## KEYWORDS

Ischemic colitis, fruquintinib, VEGFR inhibitor, gastrointestinal bleeding, targeted therapy toxicity

## LEARNING POINTS

- Vascular endothelial growth factor receptor tyrosine kinase inhibitors, including fruquintinib, may predispose to ischemic colitis through microvascular dysfunction, even in the absence of large-vessel occlusion or traditional ischemic risk factors.
- Ischemic colitis should be considered in patients receiving or recently exposed to anti-angiogenic therapies who present with acute haematochezia and segmental colitis, despite delayed symptom onset after drug discontinuation.
- Early recognition, exclusion of alternative aetiologies, and prompt withdrawal of the suspected agent with supportive management can lead to favourable outcomes and may prevent progression to perforation or surgical intervention.

## INTRODUCTION

Fruquintinib is an oral vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 tyrosine kinase inhibitor approved for refractory gastrointestinal malignancies, including metastatic colorectal cancer. Reported adverse effects primarily include hypertension, palmar–plantar erythrodysesthesia, proteinuria, abdominal pain, diarrhoea, and fatigue[1,2]. While ischemic colitis has been reported

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with other vascular endothelial growth factor (VEGF) pathway inhibitors, such as bevacizumab, its association with fruquintinib remains poorly defined in both clinical trials and post-marketing surveillance[3]. We describe a case of severe acute ischemic colitis temporally associated with fruquintinib exposure in a patient with metastatic ampullary adenocarcinoma, highlighting a potentially underrecognized gastrointestinal complication of VEGFR inhibition.

## CASE DESCRIPTION

A 67-year-old woman with metastatic intestinal type ampullary adenocarcinoma with liver and lung metastasis, previously treated with multiple chemotherapy regimens, was enrolled in a clinical trial and initiated on fruquintinib at a reduced dose of 3 mg daily. Dose reduction from the standard starting dose of 5mg was chosen given her recent episode of haemoptysis, the presence of a new pulmonary mass, and her heavily pretreated disease course. The medication was self-discontinued after approximately one week due to significant fatigue. She had no prior history of ischemic colitis, inflammatory bowel disease, abdominal or pelvic radiation, or known hypercoagulable disorders. Prior oncologic therapies did not include other VEGF or VEGFR inhibitors within the preceding three months.

Approximately four weeks after discontinuation of fruquintinib, she presented with one day of crampy lower abdominal pain, loose stools, and an estimated 500 ml of bright red blood per rectum over 24 hours. She denied fevers, chills, nausea, vomiting, recent travel, sick contacts, and recent exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics, as well as use of anticoagulants, antiplatelet agents, vasoconstrictive medications, illicit drugs, or herbal supplements.

On admission, she was afebrile and hemodynamically stable, with a haemoglobin level of 9.4 g/dl, leucocytosis, and mild hyponatremia. Platelet count, coagulation studies, serum creatinine, lactate, liver function tests, and lipase were within normal limits. Physical examination revealed mild left lower quadrant abdominal tenderness without guarding or peritoneal signs. Computed tomography angiography of the abdomen showed a small contrast blush in the mid descending colon and segmental circumferential wall thickening with mucosal hyperenhancement and pericolonic fat stranding involving the descending and sigmoid colon, consistent with colitis *(Fig. 1)*. The mesenteric arteries and veins were patent, with no evidence of arterial occlusion, venous thrombosis, pneumatosis, or portal venous gas.

Colonoscopy was performed the following day and demonstrated severe circumferential ulceration with deep, punched out ulcers, pale and oedematous mucosa, and sharply demarcated involvement of the descending and sigmoid colon, findings highly suggestive of severe acute ischemic colitis *(Fig. 2)*. The rectum and visualized proximal colon appeared relatively spared. Due to the extent of ulceration and concern for impending perforation, the procedure was aborted in the descending colon, and biopsies were deferred.

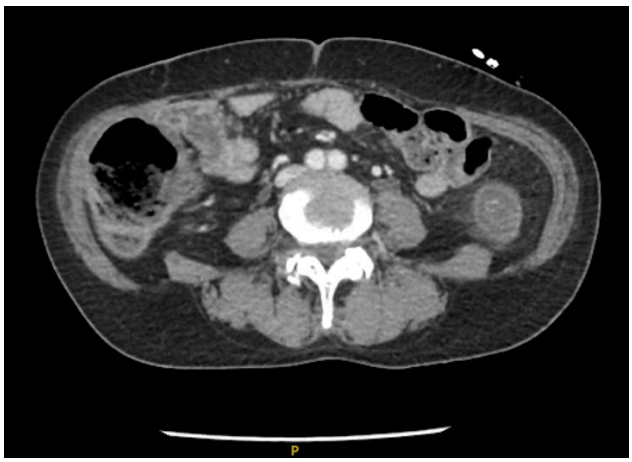


*Figure 1. Computed tomography angiography showing colonic wall thickening and pericolonic fat stranding in the descending and sigmoid colon, with focal contrast blush.*



*Figure 2. Colonoscopy of the descending colon demonstrating severe, circumferential deep ulceration, consistent with ischemic colitis.*

An infectious evaluation, including a stool polymerase chain reaction test, was negative, effectively excluding common bacterial, viral, and parasitic aetiologies. Blood cultures remained negative. Electrocardiography demonstrated normal sinus rhythm, and there was no history of atrial fibrillation, valvular disease, or heart failure to suggest a cardioembolic source. There were no documented episodes of hypotension, shock, dehydration, or vasopressor exposure preceding symptom onset. Given concern for severe colitis in an immunocompromised host, the patient was managed with intravenous fluids, bowel rest, close haemoglobin monitoring without transfusion, and empiric piperacillin-tazobactam due to the severity of colitis and concern for bacterial translocation despite negative infectious testing. Her abdominal pain and haematochezia resolved within 72 hours, with supportive care alone. She was discharged on a short course of oral antibiotics and counselled to avoid NSAIDs, with permanent discontinuation of her targeted therapy in coordination with her oncology team.

## DISCUSSION

We report a case of severe acute ischemic colitis likely associated with prior fruquintinib exposure. While ischemic colitis has not been well described in the peer reviewed literature with fruquintinib, it has been reported with other VEGF pathway inhibitors, particularly bevacizumab. Prior reports suggest that VEGF blockade may impair intestinal microvascular perfusion and delay mucosal healing, predisposing susceptible patients to colonic ischemia[3,4]. The proposed mechanism underlying ischemic complications involves VEGFR inhibition mediated vasoconstriction, regression of microvasculature, and impaired angiogenesis. Hypertension, occurring in 33–38% of patients treated with fruquintinib, and arterial thromboembolic events, reported in 0.8%, may further compromise intestinal perfusion[1,2]. A recent post marketing report of renal limited thrombotic microangiopathy further supports the potential for microvascular injury with fruquintinib[5].

Although fruquintinib was discontinued approximately four weeks prior to presentation, delayed vascular toxicities have been described with antiangiogenic agents, likely reflecting persistent endothelial dysfunction following drug exposure[6]. While causality cannot be definitively established, alternative aetiologies were systematically excluded, and the segmental distribution, characteristic endoscopic findings, and clinical course were most consistent with acute ischemic colitis. Histopathologic confirmation was deferred due to concern for perforation, representing a limitation of this report.

As the use of VEGF and VEGFR inhibitors continues to expand across oncologic indications, clinicians must remain alert for ischemic complications, particularly in patients with underlying vascular risk factors or prior treatment related vascular compromise. Prompt evaluation and withdrawal of the suspected agent are recommended in the management of severe treatment related gastrointestinal toxicity and may prevent progression and reduce morbidity[7,8]. This case contributes to the emerging safety profile of VEGF pathway inhibition and underscores the importance of continued post marketing surveillance.

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