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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Tofacitinib-Associated Cerebral Venous Sinus Thrombosis

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ABSTRACT

Tofacitinib is a Janus kinase inhibitor indicated to treat adult patients with moderately to severely active ulcerative colitis (UC). Although thrombosis is a known adverse event of tofacitinib, there are no reports specific to cerebral venous sinus thrombosis (CVST). We present a report of a patient presenting with a CVST several months after starting tofacitinib. Initially, this 60-year-old man with poorly controlled UC who previously had a nonthrombotic hemorrhage was found to have venous sinus thromboses of the right transverse and sigmoid sinuses. Hematological workup did not reveal any underlying hypercoagulable conditions, aside from UC. This is the first report of a patient with CVST likely resulting from the Janus kinase inhibitor tofacitinib. This case report should prompt compilation of all thrombotic events in patients receiving tofacitinib.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a particular type of stroke, less common and distinct from arterial strokes. It represents about 0.5% to 1% of all reported strokes and occurs because of thrombosis of the dural venous sinuses and/or cerebral veins, leading to venous congestion, raised intracranial pressure, ischemia, or intracerebral hemorrhage.[1–3] Diagnosis is typically made using magnetic resonance imaging/magnetic resonance venography (MRV) imaging. Risk factors include hereditary thrombophilia, infection, systemic diseases such as cancer and antiphospholipid antibodies, and medications such as oral contraceptives.[4] Tofacitinib is a Janus kinase (JAK) inhibitor indicated to treat adult patients with moderately to severely active ulcerative colitis. It holds a black box warning for thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis. This adverse event is reported more commonly in patients treated with the tofacitinib 10-mg twice-daily dosing as compared to the 5-mg twice-daily dosing.[5] Although thrombosis is a known adverse event of tofacitinib, there are no reports specific to CVST. We present a report of a patient presenting initially with a subarachnoid hemorrhage who was then found to have a CVST 6 weeks after hospital discharge.

CASE REPORT

A 60-year-old man with a medical history of gout, hypertension, and ulcerative colitis diagnosed by colonoscopy 2 years earlier. He had been prescribed a variety of medications including oral and rectal mesalamine, oral budesonide, and adalimumab injections. He did not have control of disease with these therapies, and his rectal stool studies revealed a calprotectin level of greater than 1,000 μg/g, indicating that there was still a large amount of inflammation in the colon. Because of these findings, he was started on tofacitinib 10 mg twice daily for better control of his ulcerative colitis. The higher dose was chosen as the recommended induction therapy for the first 8 weeks. This regimen provided him control of his ulcerative colitis. He had not yet been switched to the maintenance therapy dosing of 5 mg twice daily.

Three months after the initiation of the tofacitinib, he presented to the emergency department complaining of the "worst headache of his life" for 2 days with associated nausea and vomiting. He had no known neurologic history before presentation. Computed tomography of the head revealed subarachnoid hemorrhage (SAH) in the prepontine cistern and intraventricular hemorrhage in the bilateral occipital horns of the lateral ventricles with mild associated hydrocephalus. Computed tomography angiography (CTA) of the head and neck with and without contrast revealed no aneurysm, arteriovenous malformation, or fistula to explain SAH. Magnetic

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resonance imaging with and without contrast showed no further significant findings. The patient underwent a diagnostic cerebral angiogram which confirmed no arterial malformation or aneurysm, and cerebral sinuses and veins were unremarkable. He did not undergo a hematologic workup at this time because it is not indicated in the setting of spontaneous intracranial hemorrhage which is known to be secondary to a venous source. Baseline laboratory values did not show any indication of an increased risk of bleeding.

The patient was discharged home with the diagnosis of spontaneous perimesencephalic SAH and continued on tofacitinib for his ulcerative colitis since it is not known to cause SAH. He presented 6 weeks later for routine follow-up with repeat CTA of his head. This demonstrated new findings of dural venous sinus thrombosis of the right transverse and sigmoid sinuses, with resolution of SAH. Given new findings of cerebral venous and sinus occlusion, a repeat cerebral angiogram was performed confirming CTA findings. Aside from his ulcerative colitis, he did not have any other personal or family history of a hypercoagulable state.

Tofacitinib was switched to ustekinumab secondary to the known adverse effect of thrombosis and suspicion that its use also contributed to the formation of cerebral venous sinus thrombosis. The repeat catheter angiography ruled out any underlying vascular pathology before initiation of anticoagulation given his recent SAH and showed complete occlusion of his right transverse sinus with good collateral flow into his venous system, and a follow-up MRV revealed stable findings. A hypercoagulable workup of factor V Leiden, Lupus anticoagulant, prothrombin gene mutation, antiphospholipid antibodies, homocysteine, protein C and S, erythrocyte sedimentation rate, and antinuclear antibody did not reveal any other underlying hypercoagulable conditions. The patient has been continued on rivaroxaban for anticoagulation until MRV follow-up in 6 months.

DISCUSSION

This unique case revealed the presence of cerebral venous sinus thrombosis in a patient with recent spontaneous intracranial hemorrhage. No underlying hypercoagulable condition or vascular pathology was identified as the cause of his cerebral venous sinus thrombosis. The thrombus was not present at the time of intracranial hemorrhage, as evidenced on cerebral angiogram. Therefore, it is unlikely that the new thrombus was the cause of SAH. We have concluded that the SAH was an independent finding.

Our patient had a long-standing history of ulcerative colitis that was treated with tofacitinib. Given the new findings of cerebral venous sinus thrombosis, tofacitinib was discontinued as a possible contributing or causative factor, and the patient was changed to ustekinumab. A growing body of evidence suggests that JAK inhibitors may not be suitable for patients at risk of thromboembolic events. The mechanism of thromboembolism is currently unknown, but a systemic review of the Food and Drug Administration's Adverse Event Reporting System found elevated reporting for thromboembolic adverse events for the entire class of JAK inhibitors. Most events reported have been pulmonary thrombosis, pulmonary embolism, deep vein thrombosis, and portal vein thrombosis. There have been no reports, to the best of our knowledge, of CVST. Conditions associated with CVST can be classified as predisposing or precipitating. In this case, the patient had a precipitating condition of taking a medication with a prothrombotic action. He did not have any other predisposing risk factors or conditions that could have been attributed to this event.

Although tofacitinib is associated with an increased risk of thrombosis, this is the first report of a patient with CVST with concomitant use of tofacitinib. This case report should prompt investigations of tofacitinib on hypercoagulability to determine whether this contributed to the formation of venous sinus thrombosis.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. N. Gofman is the article guarantor.

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Informed consent could not be obtained from the patient despite several attempts. All identifying information has been removed from this case report to protect patient privacy.

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