A Rare Case Of Cerebral Venous Thrombosis During An Inflammatory Bowel Disease Flare-Up
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INTRODUCTION
Inflammatory bowel disease is group of inflammatory disorders involving small intestine and colon. Ulcerative colitis (UC) and Crohn’s disease are the two main types of IBD and have a variety of involvement outside of the gastrointestinal tract as well, termed extraintestinal manifestations. These manifestations include involvement of the musculoskeletal, hepatobiliary, and pulmonary systems, skin, eye, and coagulation cascade. When the coagulation cascade is affected, a state of hypercoagulability may result in venous thromboembolism. Thromboembolism is a complication seen in 0.7 to 7.7% of IBD patients during flare-ups and mainly involves pulmonary vasculature and deep veins of the legs [1, 6, 7, 8]. Cerebral venous thrombosis (CVT) is a rare complication in the setting of an IBD flare, with an annual incidence of 3-4 cases per million [2, 5]. It is more prevalent in patients less than 40 years of age and in females. It is a potentially fatal complication with more than 80% of patients developing permanent sequelae or death [3]. The exact mechanism of the hypercoagulable state during the IBD flare is poorly understood.

Occlusion of the cerebral venous system by the thrombosis may lead to increased pressure in the venous system resulting in decreased cerebral perfusion, ischemic injury, parenchymal hemorrhage, injury to the blood-brain barrier and vasogenic edema [2, 5]. Patients present with various symptoms including headache, seizures, encephalopathy or focal neurological signs [2, 5]. Headache is seen in 70-90% of cases and seizures are seen in 40% of cases [4]. These symptoms may closely mimic other neurological disorders and therefore the diagnosis of CVT is often misdiagnosed or missed [4]. A high index of suspicion is needed to make a prompt diagnosis in order to initiate the appropriate treatment. Here, we present a case of a patient who developed acute encephalopathy in the setting of an IBD flare and was found to have CVT.

CASE REPORT
A 38-year-old right-handed Caucasian female with a seven-year history of ulcerative colitis managed with 6-mercaptopurine and prednisone for the past four years presented to the Emergency Department (ED) with a one-day history of altered mental status, aphasia and generalized weakness. She recently had developed a flare-up of ulcerative colitis during which she was having about 20 bowel movements a day and episodes of vomiting. She was seen by her gastroenterologist and her daily oral prednisone dose was increased. Her diarrhea and vomiting symptoms improved significantly; however, she developed altered mental status and was referred to the ED. On presentation, she was disoriented to place and time, her pupils were equal and reactive, and she had a right-sided Babinski sign. Initial laboratory tests showed a white blood cell count of 14,000, hemoglobin of 13.5 g/dL, and platelet count of 220,000. Computed tomography (CT) scan of the head showed a large area of hypodensity in the left temporal lobe with associated surrounding vasogenic edema and an area of intraparenchymal hemorrhage. Magnetic resonance imaging (MRI) of the brain confirmed the presence of a large cerebral venous thrombosis (CVT) associated with intraparenchymal hemorrhage and surrounding vasogenic edema in the left temporal lobe extending to the parietal lobe. This finding of venous thrombosis was suspected to be from a hypercoagulable state associated with IBD flare-up.
mental status and aphasia three days later prompting her spouse to bring her to the ED.

In the ED, Computed Tomography (CT) scanning of her head was performed which revealed a large intraparenchymal hemorrhage in the left temporal area with surrounding edema (Figure 1a). She was admitted to the surgical intensive care unit for hemodynamic monitoring and possible neurosurgical intervention. She was started on Levetiracetam for prophylaxis of seizures. Computed Tomography Angiography (CTA) of her brain did not show any signs of arterial occlusion, aneurysm or vascular malformation; however, a lack of contrast enhancement was noted in the left transverse and sigmoid sinuses and the proximal left internal jugular vein, raising strong suspicion for sinus thrombosis (Figure 1b). Therefore, Magnetic Resonance Venography (MRV) and Magnetic Resonance Imaging (MRI) of the brain were performed the following day. MRV was consistent with occlusion of the left transverse and sigmoid sinuses through the jugular bulb and foramen, confirming the suspicion for sinus thrombosis (Figure 1c). The MRI demonstrated a previously visualized large hemorrhage with surrounding vasogenic edema in the left temporal lobe extending to the parietal lobe. It also showed a 5.5mm left-to-right subfalcine herniation at the septum pellucidum and the beginning of uncal herniation (Figure 1d). Despite the large intraparenchymal hemorrhage, she was started on heparin drip for sinus thrombosis.

The next hospital day, patient had an acute episode of peripheral vision loss prompting a repeat CT of the head which showed the previously identified hemorrhagic infarct and a new finding of a moderate amount of blood filling the left ventricle and a small amount in the right ventricle (Figure 1e). Therefore, she was started on hypertonic saline and was continued on it for two days. She gradually made improvements with her speech but was still having difficulty identifying certain words and therefore was started on aggressive physical, occupational and speech therapy.

Her cerebral venous thrombosis (CVT) in the setting of IBD flare was suspected to be from a hypercoagulable state. Therefore, a hypercoagulable workup was done and showed increased level of Clotting Factor VIII, decreased level of Protein C and a positive Lupus Anticoagulant test. She was started on Warfarin with an INR goal of 2-3. Additional workup during her hospital stay included a CT of her abdomen/pelvis for future consideration of colectomy. CT showed evidence of moderate wall thickening and distension of the transverse colon and no involvement of terminal ileum, consistent with the findings seen in ulcerative colitis. Once she was stable, she was discharged home with instructions for close follow-up with her gastroenterologist and neurologist. An MRV of her brain was repeated five months later which did not show any new changes (Figure 1f).

DISCUSSION
Cerebral venous thrombosis is a rare complication of IBD and is associated with a poor outcome. Since the presenting symptoms can be highly variable, it becomes very difficult to make the diagnosis on time. When evaluating patients that present with neurological symptoms in the setting of an IBD flare, physicians need to be wary for the possibility of CVT. Although head CT has poor sensitivity for detecting CVT, it is usually the most frequent imaging test performed on a
patient with neurological symptoms. In about one third of cases, CT may actually show signs of CVT including hyperdensity in area of a sinus or cortical vein and filling defects in superior sagittal sinus [5]. MRI combined with MRV is the most sensitive test for detection of CVT and therefore, the American Heart Association and American Stroke Association recommend MRI with T2-weighted imaging and MRV in patients with suspected CVT [5]. The thrombus may be directly visualized as a hypodense area in cerebral veins on T2-weighted images [5].

Although the exact mechanism that leads to the hypercoagulable state in IBD flare is poorly understood, various mechanisms may play a role including hypercoagulation (elevated clotting factor VIII, fibrinogen, decreased protein C and protein S), hypofibrinolysis, platelet abnormalities, endothelial dysfunction, and immunological abnormalities (anti-phospholipid antibodies) [4, 9]. Studies have shown that inflammatory cytokines can affect the coagulation cascade at different points and alter platelet function which may partly explain the hypercoagulability during the active IBD [1]. Factor VIII may be elevated in up to 50% of patients during ulcerative colitis flare-ups [1]. However, no specific factor has been shown to act as a consistent marker for detecting the hypercoagulable state of IBD [1]. Nevertheless, hypercoagulability work-up is recommended.

It is crucial to make a prompt diagnosis of CVT and start appropriate management as it can lead to a catastrophic outcome. There have been studies that show overall mortality to be as high as 25% from thromboembolism [1]. In a large study on patients with CVT, the mean 30-day mortality was found to be 5.6% [2]. A major cause of mortality is related to herniation from the unilateral mass effect and therefore requires prompt treatment [2]. The role of anticoagulation has been controversial especially in the patients who are at risk or suspected to have a hemorrhagic infarct. In selected patients, including our patient, anticoagulation even in the setting of a hemorrhagic infarct, has been shown to be very effective with a positive outcome. Although there are no established guidelines, anticoagulation using intravenous heparin or subcutaneous low-molecular-weight heparin until the patient is stable, followed by oral anticoagulation for 3-6 months have been an effective treatment strategy [6]. In patients who do not respond to anticoagulation, more advanced techniques such as direct thrombolytic therapy, endovascular treatment or surgical interventions may be considered [5, 6].

In our case, the patient’s MRI showed evidence of left-to-right subfalcine herniation as well as the beginning of an uncal herniation. The patient was started on intravenous heparin despite the presence of hemorrhagic infarct. She was treated successfully with anticoagulation and had a positive outcome. Additionally, a hypercoagulable workup that was done showed an increased level of Clotting Factor VIII, decreased level of Protein C and a positive Lupus Anticoagulant test. Therefore, long-term warfarin with an INR goal of 2-3 was initiated. This case signifies the importance of detecting CVT on time and beginning appropriate treatment. The important association between IBD and the hypercoagulable state during a flare needs to be recognized by primary care physicians. Administration of venous thromboembolism prophylaxis during IBD flare may be beneficial in reducing catastrophic events. However, it may not be cost effective as shown by Nguyen et al [10]. More studies need to be done to establish a guideline.

References
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