

Inflammatory Bowel Disease and Cerebral Venous Sinus Thrombosis

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Thromboembolic events are a known and potentially life-threatening extraintestinal manifestation of inflammatory bowel disease (IBD). The overall incidence of thrombosis in IBD is estimated to be between 1.3% and 7.5%.^{1,2} Reported cases of thrombosis are arterial or venous and occur most frequently in the deep leg veins and/or pulmonary vasculature. Unusual but reported sites of venous thrombosis include the cerebral sinuses, retinal vessels, and the heart. Although associations have been described between IBD and inherited prothrombotic states, the exact pathophysiology of thromboembolism in IBD remains unknown.

We present two cases of cerebral venous sinus thrombosis (CVST) in patients with IBD. A literature search of IBD and CVST yielded 31 additional cases (Table 1).³⁻²⁹ The literature is reviewed including a discussion about presentation and treatment of CVST as well as current theories about thrombosis and IBD.

Case Reports

Case #1: JB

A 23-year-old nonsmoking woman, diagnosed with biopsy-confirmed ulcerative colitis (UC) at the age of 16, presented with headache, nausea, and vomiting of 3 days duration. The headache was located behind her eyes and in her neck. Associated symptoms included nausea and vomiting but no seizure activity, paresis, mental status changes, or photophobia. She was in the process of evaluation for colectomy due to persistent pancolitis and had received past treatment with azathioprine, mesalamine, and cyclosporine.

Her medical history was complicated by a deep venous thrombosis 10 months prior, suspected to be secondary to oral-contraception use. The earlier episode of thrombosis occurred concurrent with an acute flare.

A hypercoagulable work-up administered at the time was negative. She was treated successfully with 6 months of heparin and low-molecular weight heparin and oral contraception was stopped.

On present physical examination, she was febrile to 38.8° C but otherwise stable. Her examination was unremarkable except for decreased range of neck motion due to pain. She showed no evidence of frank meningismus, photophobia, or neurologic deficits. Laboratory tests revealed a white blood cell count of 4,200 cells/ μ L, hemoglobin of 9.9 g/dL, and hematocrit of 29.6%. A lumbar puncture on admission was negative for meningitis and she proceeded to imaging studies. Magnetic resonance imaging (MRI) revealed acute bilateral maxillary sinusitis and left-sided otitis media with extension of infection to the left tentorium. An incidental note was made of a filling defect within the left lateral sinus. A magnetic resonance venogram (MRV) confirmed occlusion of the transverse sinuses and sigmoid sinuses. Finally, cerebral angiography (Figure 1) showed thrombosis of the left transverse sinus and cavernous sinus, and compromised but patent right transverse sinus, sigmoid, and right jugular veins.

Initially, it was thought that the venous thromboses were secondary to otitis media and sinusitis and the patient was treated with intravenous (IV) antibiotics with some improvement in her headache. Anticoagulation was not initiated due to the concern for intracerebral bleeding. However, she re-presented 5 days later with worsening headache and neck stiffness as well as a fever, despite administration of broad-spectrum antibiotics. She received intravenous heparin and warfarin with complete resolution of her headache and neck stiffness. A hypercoagulable work-up was negative for proteins C and S, Factor V Leiden, antithrombin III, homocysteine, antiphospholipid antibody syndrome, and prothrombin gene mutation during this hospitalization.

Case #2: SG

A 16-year-old nonsmoking male with biopsy-confirmed Crohn's disease, involving the terminal ileum and diag-

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Table 1. Reported Cases of Cerebral Venous Sinus Thrombosis and Inflammatory Bowel Disease

Reference	Age	Sex	IBD	Location	Treatment
Case report 1	23	F	UC	Transverse & sigmoid	Heparin
Case report 2	16	M	CD	Superior sagittal	Heparin
Harrison ³	54	F	UC	Left superficial cortical	-
Harrison ³	34	M	UC	Left sigmoid	-
Kalbag ⁴	8	M	UC	Superior longitudinal	-
Borda ⁵	23	M	UC	All major venous sinuses (autopsy)	Dexamethasone
Lam ⁶	28	F	UC	Cerebral thrombosis	-
Rousseau ⁷	18	M	UC	Superior longitudinal	Anti-convulsants
Sigsbee ⁸	30	F	RE	Sagittal	-
Yerby ⁹	28	M	UC	Superior sagittal	-
Bewermeyer ¹⁰	35	F	UC	Superior sagittal and temporal	-
Usui I ¹¹	19	M	UC	Superior sagittal	-
Markowitz ¹²	14	M	UC	Left sigmoid and lateral	Anti-convulsants
Johns ¹³	33	F	UC	Superior sagittal/transverse	-
Garcia-Monco ¹⁴	44	F	CD	Superior sagittal and right lateral	Dexamethasone
Korsten ¹⁵	40	M	UC	Cavernous	Heparin
Moriyama ¹⁶	27	M	UC	Left transverse	-
Cecchi ¹⁷	26	M	UC	Superior sagittal	Heparin
Musio ¹⁸	24	M	UC	Superior sagittal	ASA/anti-convulsants
Fukudome ¹⁹	33	M	UC	Superior sagittal	-
Papi ²⁰	33	F	UC	Superior and inferior long dural	ASA
Bridger ²¹	14	F	UC	Widespread venous thrombi	-
Gonera ²²	30	F	UC	Superior sagittal	LMWH
Jackson ²³	57	n/a	CD	Cerebral NOS	-
Jackson ²³	45	n/a	UC	Cerebral NOS	-
Jackson ²³	53	n/a	UC	Cerebral NOS	-
Jackson ²³	82	n/a	UC	Cerebral NOS	-
Derdeyn ²⁴	26	F	UC	Cortical vein	-
Alacade-Encinas ²⁵	19	M	UC	Left transverse and superior longitudinal	Heparin
Bansal ²⁶	30	M	UC	Sagittal	Heparin
Tsujikawa ²⁷	27	M	UC	Superior sagittal	Heparin & urokinase
Al-Malik ²⁸	14	M	UC	Superior sagittal & left lateral sigmoid	LMWH
Srivastava ²⁹	29	M	UC	Superior sagittal & left lateral sigmoid	LMWH

ASA = aspirin; CD = Crohn's disease; LMWH = low molecular weight heparin; N/A = not available; NOS = not otherwise specified; RE = regional enteritis; UC = ulcerative colitis.

nosed at the age of 12, presented with lethargy, significant anemia, and severe headaches of several weeks duration. There was no seizure activity or focal neurologic deficit noted on presentation. Small bowel follow-through revealed a 10-cm area of terminal ileum with stricture, an inflammatory mass, and entero-enteric fistulas. Medical management of his CD included azathioprine, prednisone, and mesalamine.

On physical examination, he was afebrile with stable vital signs. Examination revealed right lower quadrant abdominal pain with normal neurologic findings. His white blood cell count was 10,000 cells/ μ L, hemoglobin measured 10.3 g/dL, and hematocrit 31.6% after transfusion. Lumbar puncture was not performed. MRI revealed superior sagittal sinus and bilateral transverse sinus thrombosis. He was anticoagulated with heparin initially and maintained on warfarin with marked improvement in his headaches over several days. MRI performed 1 month after initiating anticoagulation showed evidence of recanalization of the superior sagittal sinus. Hypercoagulable workup revealed positive anticardiolipin antibodies.

Discussion

CVST is a recognized thrombotic complication of IBD. Although most cases have been reported in patients with UC, CVST is also seen in patients with Crohn's disease. A majority of cases involve the dural sinuses. The most commonly reported site of dural sinus thrombosis is the sagittal sinus. In this review of 33 reported cases, the median age of onset of thrombosis is 28 years, with a male to female ratio of 1.6:1. The presenting symptom of CVST in both of our case reports was severe headache. This is consistent with a prospective study of 59 patients with CVST (of any cause) that also found headache to be the presenting complaint in 95% of cases.³⁰ Other, less common, presentations included focal seizures with or without secondary generalization (47%), unilateral or bilateral paresis (43%) and papilledema (41%).³⁰

CVST is diagnosed with an imaging study showing a filling defect. Currently, the preferred diagnostic modality is MRI.³¹ Cerebral angiography and computed tomography contrast venography have also been used. Lumbar puncture is often done in the work-up of headache to exclude infectious etiologies, though there are no specific cerebral spinal fluid abnormalities associated with CVST.

The etiology of thromboembolism including CVST in patients with IBD remains unclear. There are studies that implicate hypercoagulability in the pathogenesis of IBD, whereas others relate prothrombotic inherited states with IBD. Investigators have looked at IBD and hyperhomocysteinemia, Factor V Leiden, activated protein C, prothrombin mutations, anticardiolipin antibodies,

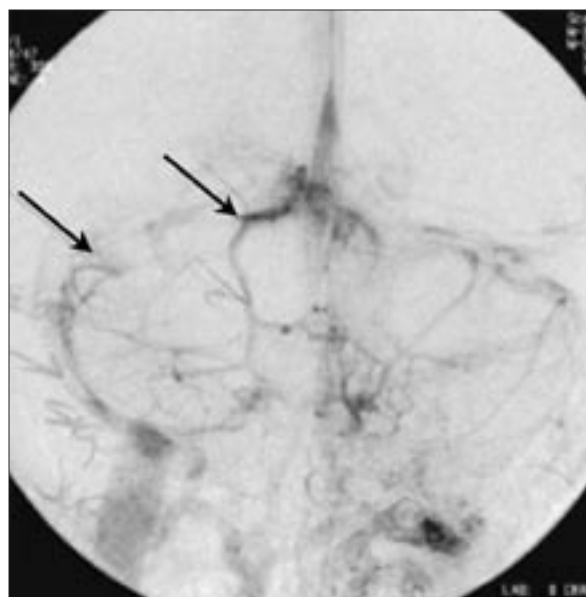


Figure 1. Anteroposterior projection in the venous phase of a left vertebral angiogram 6 days after presentation showing no opacification of the left transverse sinus (between arrowheads).

antithrombin III deficiency, and protein S deficiency. Despite many studies in this field, the incidence and mechanism of inherited prothrombotic states in IBD remains incompletely understood and controversial. Furthermore, although we did so in our two cases, it is unclear if IBD patients with thromboembolic events including CVST should be screened for inherited prothrombotic states. Current guidelines suggest screening in any patient with thromboembolism who is less than 50 years old, has a family history of venothromboembolism among one or more first degree relatives, has unusual sites of spontaneous thrombosis (which include CVST), or has had a massive venous thrombosis. We suggest testing for prothrombotic states in IBD patients who present with CVST because a positive result (as discovered in 1 of our patients) would require prolonged anticoagulation and have implications for further testing in family members.

Presently, there are no accepted guidelines for management of patients with CVST. Recent studies suggest that anticoagulation, even in patients with evidence of hemorrhage, is associated with improved survival and resolution of symptoms.^{32,33} A single, randomized trial compared intravenous heparin with placebo in the treatment of venous sinus thrombosis of any cause, though it is not stated specifically if patients with IBD were included. The study was stopped after only 20 patients were enrolled due to deaths in the nonanticoagulated group. Eight of 10 patients in the heparin group recovered complete neu-

rologic function, whereas only 1 patient in the placebo group did. There were no deaths in the heparin group and 3 in the placebo group.³² Another trial compared low-molecular weight heparin (LMWH) to placebo for 3 weeks in the treatment of CVST. There was no benefit seen in the LMWH group, though there was no increased risk of hemorrhage either.³³ Meta-analysis of these trials shows that with heparin therapy there is a 70% relative risk reduction of death and a 56% reduction of death or dependency compared to placebo.³⁴

Of the cases presented in this review, eight were successfully treated with anticoagulation, but it remains unclear how long to continue anticoagulation. For patients with deep venous thromboembolism or pulmonary embolism, the duration of anticoagulation depends on risk factors such as presence of a hypercoagulable state, cancer, age of the patient, and additional risks of clotting such as smoking.³⁵ Patients with IBD and thrombosis have chronic risk factors due to their systemic disease and should remain on anticoagulation therapy for at least 12 months and perhaps indefinitely.

Although treatment with heparin is accepted, the use of thrombolytics for CVST remains controversial. A retrospective study comparing local urokinase therapy with systemic heparin in 40 patients with superior sagittal sinus thrombosis found no statistical difference in hemorrhagic complications and comparable neurologic outcomes.³⁶ There is one case report of successful thrombolytic therapy in CVST and UC.²⁷ Further study is needed before thrombolytic therapy can be recommended routinely.

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Review

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Thrombosis of the cerebral sinuses is a rare neurologic disease, with an estimated incidence of 3–4 per 1 million people per year. The clinical presentation is highly variable and consequently diagnosis and adequate treatment are often delayed. Therefore, it is most appropriate that Kupfer and Rubin¹ emphasize its occurrence in combination with IBD.

The many symptoms and signs of CVST can be grouped according to two different pathophysiologic mechanisms.²

1. Occlusion of the major cerebral sinuses or the jugular veins causes reduced absorption of the cerebrospinal fluid, which leads to intracranial hypertension with headache, papiledema, and sometimes abducent nerve compression. The brain parenchyma can be completely unaffected in intracranial hypertension and these patients are usually alert and appear well except for headache and occasional visual symptoms. Severe papiledema may cause sudden blindness, and the priority in these cases is to reduce intracranial pressure.
2. Occlusion of one or more cerebral veins, which causes localized cerebral edema, venous infarcts, and cerebral hemorrhage. These patients also present with headache, but there may be a plethora of neurologic signs and symptoms, depending on the localization of the lesions. Seizures occur frequently in this condition.

In many patients, intracranial hypertension and localized lesions occur simultaneously. In a subgroup of patients with extensive CVST, the combination of intracranial hypertension, generalized cerebral edema, and localized space-occupying lesions (hemorrhagic infarcts) causes a life-threatening disease, which may rapidly evolve to cerebral herniation and death.

Many different causes and conditions associated with CVST have been reported.^{3,4} They can be subdivided into inherited and acquired prothrombotic conditions, local and generalized infections, hematologic diseases, malignancies, trauma, and aseptic inflammatory diseases. Examples of the latter are systemic lupus erythematoses,

Behçets disease, and IBD. In the largest prospective study of CVST, which was published in 2004 and enrolled 624 patients, 10 patients had IBD as the main cause of their sinus thrombosis.⁵ As emphasized by Kupfer and Rubin, the exact mechanism that relates IBD to CVST is unknown. Apparently, patients with IBD have an increased generalized thrombotic risk, which usually manifests itself as leg vein or pulmonary thrombosis, and occasionally as sinus thrombosis. A number of factors may promote thrombosis in patients with IBD, such as thrombocytosis, a generalized inflammatory response, and intestinal loss of circulating anticoagulants. Treatment with corticosteroids is an additional risk factor. Interestingly, the two cases presented both have additional risk factors beyond IBD. Patient #1 had a left-sided otitis, which is a classic cause of thrombosis of the adjacent sigmoid and transverse sinuses. Patient #2 had severe anemia, which is in and of itself a factor associated with CVST.

The treatment of CVST with heparin has inspired controversy because venous infarcts tend to become hemorrhagic and many patients with CVST have intracerebral hemorrhages before treatment. Yet two small randomized trials did not show increased or new cerebral hemorrhages after heparin treatment, and patients treated with heparin tended to have better outcomes, although the effects were not statistically significant.^{6–8} Most experts now agree that full anticoagulation with conventional or LMWH is the best treatment for patients with CVST, even in the presence of baseline hemorrhagic venous infarcts. This strategy is also advocated by a recently published European guideline.⁹ The safest strategy is to anticoagulate patients before they develop hemorrhages by new venous occlusions. Therefore, early diagnosis of CVST is of paramount importance and physicians treating patients with IBD should be aware of this potentially disabling complication.

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