American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e932123
DOI: 10.12659/AJCR.932123

Received: 2021.03.12
Accepted: 2021.05.19
Available online: 2021.05.26
Published: 2021.07.05

New Horizons for Diagnostic Pitfalls of Cerebral Venous Thrombosis: Clinical Utility of a Newly Developed Cerebral Venous Thrombosis Diagnostic Score: A Case Report and Literature Review

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared
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Patient: Male, 35-year-old
Final Diagnosis: Cerebral venous
Symptoms: Bloody diarrhea • throbbing persistent headache • weight loss
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Mistake in diagnosis

Background: Diagnosing cerebral venous thrombosis (CVT) poses significant challenges owing to a nonspecific clinical presentation, poorly correlated laboratory biomarkers, and low sensitivity of non-contrast head computed tomography (CT). We describe a case of missed CVT diagnosis, due to low clinical suspicion and nonrecognition of anemia as a prothrombotic factor, especially during an ulcerative colitis (UC) flare. A recently proposed CVT clinical probability score can guide clinicians in pursuing further neurovascular imaging.

Case Report: A 35-year-old man, with treatment-naive UC, presented to the Emergency Department (ED) with new-onset diffuse headache, 4 weeks of bloody diarrhea, and weight loss. Initial ED laboratory studies revealed severe anemia and unremarkable non-contrast head CT. Two days later, the patient returned to the ED for worsening headache. Non-contrast head CT revealed a left temporal hypodensity. This was later confirmed as acute ischemia on magnetic resonance imaging (MRI). MR venogram revealed thrombosis of the left transverse and sigmoid sinuses, leading to initiation of therapeutic subcutaneous anticoagulation. Repeat MRI, secondary to worsening headache, revealed the development of petechial hemorrhages within the core of venous ischemia in the left temporal lobe. Therapeutic anticoagulation, along with symptomatic management of UC, led to clinical stabilization.

Conclusions: CVT should be suspected in patients with UC, especially in the context of anemia, presenting with new-onset or worsening headaches. Recognizing anemia as a thrombogenic factor is crucial. Diagnosis of CVT is challenging due to non-focal symptoms and poorly correlating diagnostic tests. We endorse implementing the CVT clinical probability score into AHA/ASA CVT guidelines to enhance diagnostic accuracy.

Keywords: Anemia • fibrin fragment D • Inflammatory Bowel Diseases • Stroke • Venous Thrombosis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932123

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Background

Cerebral venous thrombosis (CVT) poses a significant diagnostic challenge because of its nonspecific clinical presentation. Holocranial headache, in 90% of cases, is the most common acute presenting symptom [1], followed by seizures (generalized or focal) in about 40% of cases [1,2] and focal neurological deficits in approximately 37% of cases [3]. Diagnosis of CVT has proven to be cumbersome because there are no specific laboratory biomarkers and non-contrast head computed tomography (CT) has a low sensitivity [4,5]. Magnetic resonance imaging (MRI), CT venography, and MR venography are the criterion standard diagnostic tests for diagnosis of CVT [1]. Multiple risk factors have been associated with the pathogenesis of CVT. The correlation between inflammatory bowel disease (IBD) and CVT has been well established, and physicians should recognize IBD as a potential contributor to CVT. Misdiagnosis of CVT in patients with IBD can result in fatal consequences, with a 25% mortality rate [6].

We describe a patient with treatment-naive ulcerative colitis (UC) who presented to the Emergency Department (ED) with a new-onset headache and bloody diarrhea. Laboratory results revealed severe anemia, and after transfusion, the patient was discharged home with a diagnosis of tension headache. Two days later, he presented to the ED with worsening headache and hypersomnolence, and eventually was diagnosed with CVT. The diagnosis was initially missed due to low clinical suspicion and an unremarkable non-contrast head CT scan. This delay in diagnosis led to the development of venous ischemia, with associated petechial hemorrhage and a protracted hospitalization course. Diagnosis of CVT should be considered in patients with underlying inflammatory bowel disease (IBD) with a new-onset or atypical headache, especially in the context of severe anemia. The thrombogenic basis of anemia has been well established in the literature [6-11], but its clinical relevance has not yet been fully recognized.

A recently proposed CVT clinical probability score by Heldner et al can be implemented as a guide in the pursuance of diagnostic neurovascular imaging. We anticipate that the utilization of this score will improve diagnostic accuracy and management.

Case Report

A 35-year-old man with a history of treatment-naive UC presented to the ED with persistent new-onset holocranial headache of a throbbing quality and moderate severity. Additionally, he reported a 4-week history of bloody diarrhea and significant weight loss, for which he did not seek any medical attention. A mental status examination revealed that the patient was alert and oriented to person, place, time, and situation, with no speech impairment. A cranial nerve and sensorimotor examination was normal, with no meningeal signs. The laboratory findings from the patient's initial ED visit are listed in **Table 1**. Of note, the complete blood count (CBC) revealed severe anemia with a hemoglobin (Hb) level of 5.5 g/dL. No D-dimer level was obtained during this ED visit. A non-contrast head CT scan showed no acute intracranial abnormalities. Four units of packed red blood cells were given to the patient. His headache responded to symptomatic treatment and the administration of intravenous morphine. The patient refused further workup and was discharged home with a diagnosis of episodic tension headache.

Table 1. Patient laboratory findings on first Emergency Department visit.

Laboratory data	Day 1 – first ER visit
Complete blood count	
Hemoglobin	5.5 g/dL
Mean corpuscular volume	70.2 fl
Mean corpuscular hemoglobin	21.1 pg
Red blood cell distribution width	24.2%
Mean platelet volume	8.6 fl
Platelets	427×10^9/L
Coagulation panel	
Prothrombin time	12.2 seconds
Partial thromboplastin time	26.2 seconds
International normalized ratio	1.1

The patient returned to the ED 2 days later with a worsening headache and hypersomnolence. The laboratory findings are listed in **Table 2**. Of note, the CBC revealed an Hb level of 8.4 g/dL. A hypercoagulable panel (protein S, protein C, antithrombin III, factor VIII, antinuclear antibody, cardiolipin antibody, prothrombin G20210A, and factor V Leiden) showed no abnormalities. A non-contrast head CT scan revealed a left temporal hypodensity (**Figure 1**). Head and neck CT angiography showed no evidence of thrombosis in the intra-cranial or extra-cranial arterial circulation.

The patient was admitted for further evaluation owing to persistent symptoms and abnormal neuroimaging findings. A diffusion-weighted imaging (DWI) sequence revealed hyperintensity in the left temporal lobe, consistent with acute left temporal lobe ischemia (**Figure 2**), with no corresponding signal alteration on apparent diffusion coefficient (**Figure 3**). Fluid-attenuated inversion recovery (FLAIR) sequences revealed hyperintensity in the left temporal and occipital lobes (**Figure 4**). There was no evidence of hemorrhage on gradient echo images. MR venography of the head revealed acute venous thrombosis involving

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Table 2. Patient laboratory findings on second Emergency Department visit and admission.

Laboratory data	Day 3 – ER visit
Complete blood count	
Hemoglobin	8.4 g/dL
RBC count	3.25 million cells/mcL
Complete metabolic panel	
Sodium	137 mEq/L
Potassium	3.3 mEq/L
Glucose	106 mg/dL
Blood urea nitrogen	13 mg/dL
Creatinine	0.8 mg/dL
Aspartate aminotransferase	9 IU/L
Alanine transaminase	14 IU/L
Alkaline phosphatase	62 IU/L
Albumin	2.8 g/dL
Total protein	7 g/dL
Lipid panel	
Total cholesterol	143 mg/dL
High density lipoprotein	39 mg/dL
Low density lipoprotein	90 mg/dL
Coagulation panel	
Prothrombin time	13.4 seconds
Partial thromboplastin time	25.5 seconds
Fibrinogen	409 mg/dL
D-dimer	321 ng/mL
Other	
Erythrocyte sedimentation rate	35 mm/h
C-reactive protein	2.2 mg/dL
Hemoglobin A1c	5.2%
Vitamin B12	387 pg/mL
Homocysteine	4.0 umol/L

the left transverse and sigmoid sinuses extending into the proximal jugular bulb, with no evidence of any involvement of the deep venous system (**Figure 5**). This finding was corroborated by the CT venography of the brain revealing an absence of flow at the level of the left transverse sinus, while showing preserved flow on the right transverse sinus (**Figure 6**). A diagnosis of CVT, secondary to the procoagulant effect of UC potentiated by severe anemia, was made. Consequently, therapeutic anticoagulation with 60 mg/0.6 mL subcutaneous low-molecular-weight heparin (enoxaparin) twice daily was initiated. The patient was also started on 40 mg prednisone and 1600 mg mesalamine orally 3 times per day by the

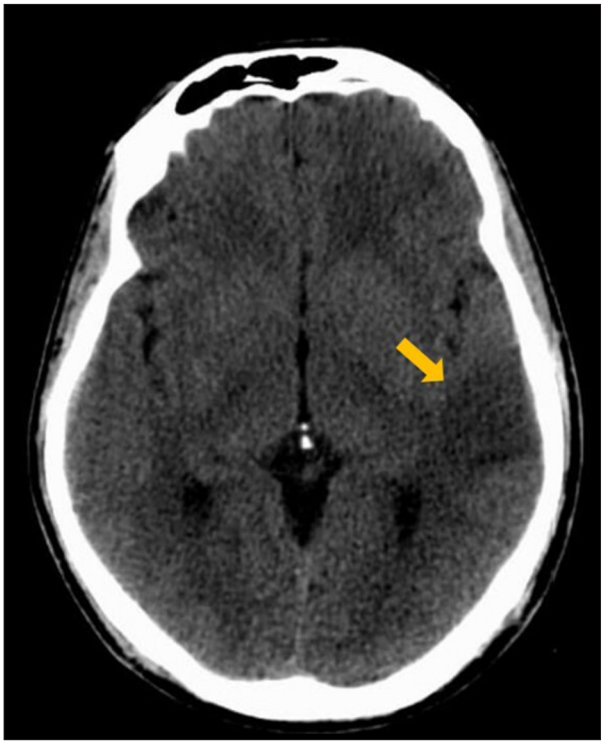

Figure 1. Non-contrast head computed tomography on second Emergency Department visit revealed hypodensity in the left temporal lobe.

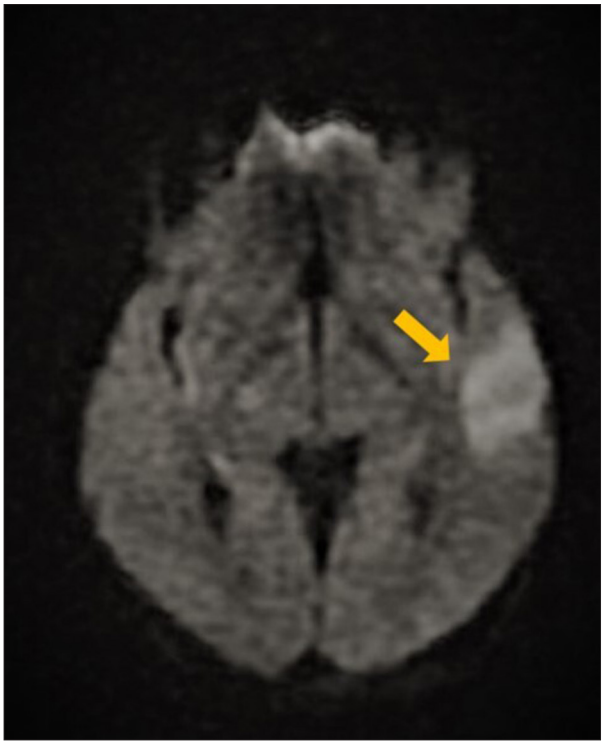

Figure 2. Diffusion-weighted imaging brain sequence on admission revealed hyperintensity in the left temporal lobe, consistent with acute ischemia.

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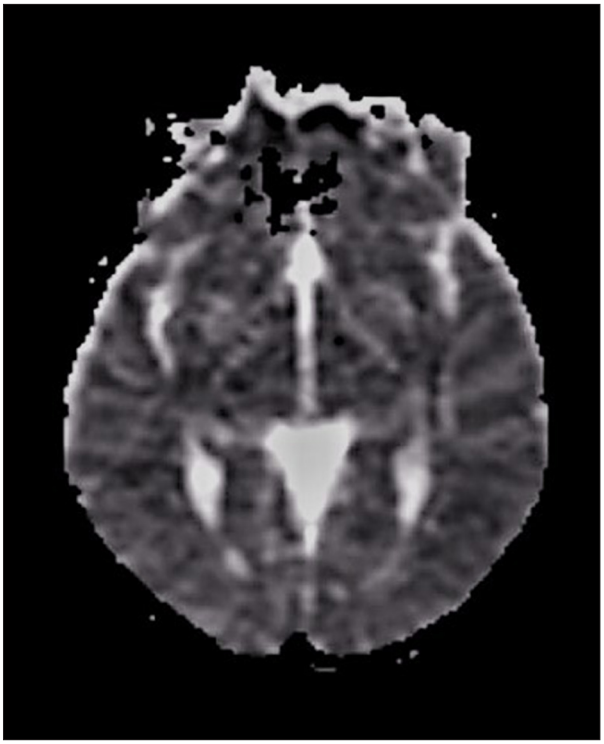

Figure 3. Apparent diffusion coefficient brain sequence on admission showed no corresponding hypodensity.

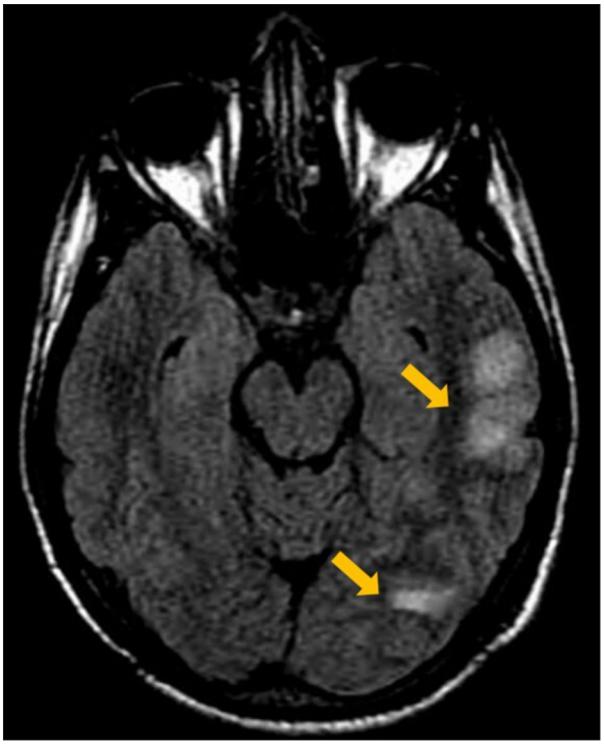

Figure 4. Fluid-attenuated inversion recovery brain sequence on admission revealed hyperintensity in the left temporal and occipital lobes.

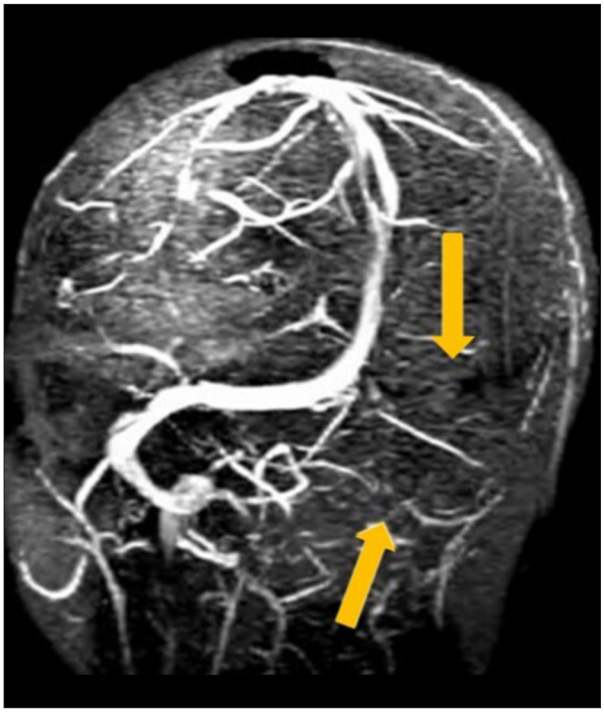

Figure 5. Magnetic resonance venography of the brain on admission revealed acute venous thrombosis involving the left transverse and sigmoid sinuses and left proximal jugular bulb.

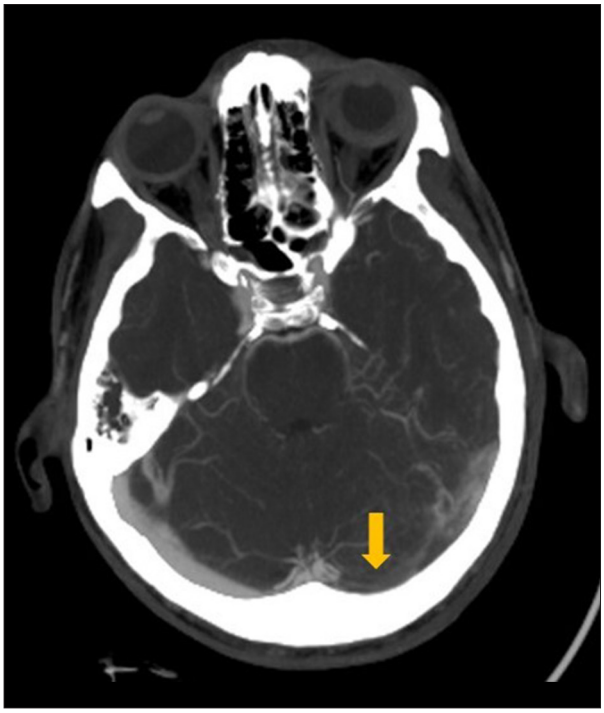

Figure 6. Computed tomography venography of the brain revealed an absence of flow at the level of the left transverse sinus, while showing preserved flow on the right transverse sinus.

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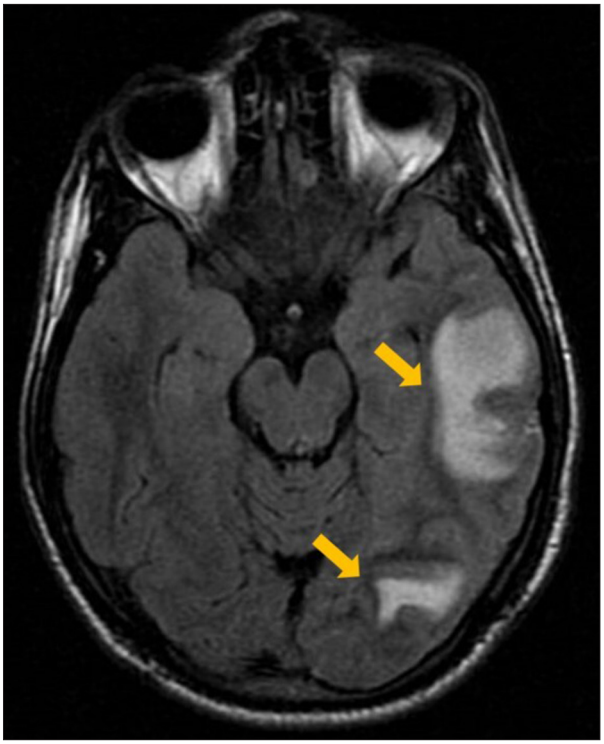

Figure 7. Fluid-attenuated inversion recovery brain repeated on day 6 of admission showed stability of the venous ischemia in the left temporal and occipital lobes.

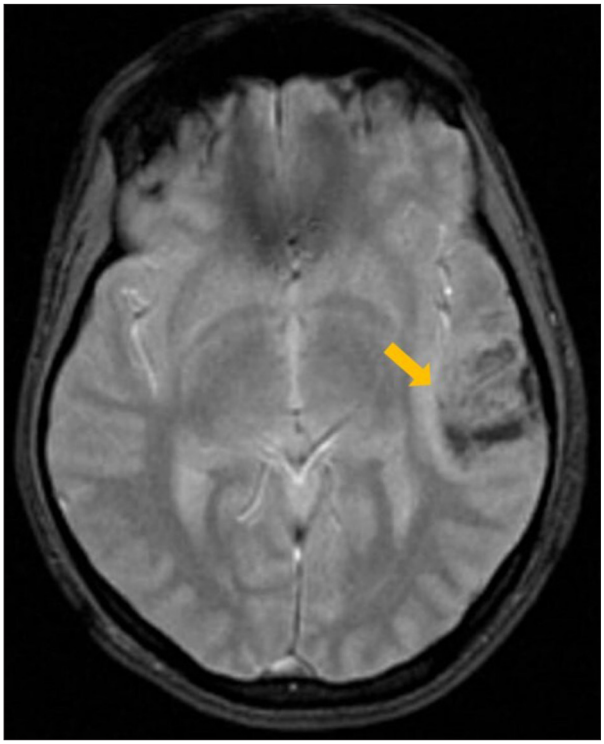

Figure 8. Gradient echo brain sequence repeated on day 6 of admission revealed the development of petechial hemorrhages within the core of the venous ischemic region of the left temporal lobe.

gastroenterologist. Worsening headache on day 6 prompted a repeat brain MRI. The DWI and FLAIR sequences show stability of venous ischemia in the left temporal and occipital lobes (**Figure 7**). Development of petechial hemorrhages within the core of the venous ischemic region of the left temporal lobe was seen on gradient echo sequence (**Figure 8**). An interdisciplinary discussion was initiated because the patient exhibited clinical and radiological deterioration. The patient and his family were consulted regarding transferring him to a higher level of care, with the option of endovascular intervention; however, the patient refused. Therapeutic doses of subcutaneous enoxaparin were continued with frequent neurological check-ups to monitor for any clinical deterioration. His headaches and hypersomnolence gradually improved, and on day 13, the patient was discharged home on warfarin 7.5 mg (target international normalized ratio [INR] 2.0-3.0), prednisone (40 mg, tapered over 3 months), mesalamine 400 mg 4 times daily, and ferrous sulfate 325 mg once daily.

On outpatient follow-up 3 months later with his primary care physician, the patient was found to be in remission, with significant weight gain and resolution of the anemia. The primary care physician ordered repeat neuroimaging; however, the patient refused additional testing. No headaches or focal neurological symptoms were reported at this visit, and the patient was lost to follow-up.

Discussion

Inflammatory bowel disease has been associated with a variety of neurological complications [12-15] (**Table 3**). One of the most serious and overlooked cerebrovascular complications of IBD is CVT [16]. IBD has a higher association with thrombosis, as compared to other systemic autoimmune disorders, such as rheumatoid arthritis and celiac disease [17-20]. Chronic IBD increases the risk of thromboembolism 3-fold, which increases to 15-fold during an active disease state [19]. Thromboembolic events can occur in up to 60% of patients during disease exacerbation or in the presence of intestinal complications, such as abscesses, fistulas, and pancolitis [6,19,20].

Harrison and Truelove (1967) were the first to report CVT in patients with UC [21]. Since then, multiple published cases have established the thrombotic complications of IBD [4,14,18,20,22]. CVT in particular is more commonly reported as a complication of IBD in the medical literature [1,5,12,13,15,16,19]. Young adults (average age, 29 years) with IBD are more prone to CVT than are young adults without IBD [6,19].

The pathogenesis of thromboembolism in IBD is not completely understood but has been hypothesized to be multifactorial [17]. IBD induces a prothrombotic state by altering levels of

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Table 3. Neurological complications of inflammatory bowel disease.

Classification	Complication
Vascular	Cerebral venous thrombosis
	Transient ischemic attack
	Cerebral infarction (Carotid thromboembolism, Cardioembolic)
	Retinal vascular occlusive disease
	Premature atherosclerosis (increased carotid artery intima/media thickness)
Immune-mediated	Cerebral vasculitis
	Optic neuritis
	Sensorineural hearing loss
	Slowly progressive myelopathy
	Melkersson-Rosenthal syndrome
	Polyneuropathy
Treatment induced	Peripheral neuropathy (Metronidazole, Infliximab, Adalimumab)
	Multifocal leukoencephalopathy (Natalizumab)/Encephalopathy (Metronidazole, Sulfasalazine)
	Central nervous system demyelination (Infliximab, Adalimumab)
	Bell's palsy (Infliximab, Adalimumab)
	Postural tremor (Cyclosporine)
	Transverse myelitis (Sulfasalazine)
Disease-related complications	Epidural/subdural spinal empyema (secondary to fistula)

the coagulation factors, decreasing fibrinolytic activity, and inducing endothelial dysfunction during the active disease state, while also promoting platelet hyperactivity, independently of the disease state [10]. Alterations to components of the coagulation cascade include increased levels of fibrinogen and factors V, VII, VIII, and XI, as well as decreased levels of factor XIII. Additionally, fibrinolysis is altered by decreased levels of tissue-type plasminogen activator, and increased production of fibrinolytic inhibitors, including plasminogen activator inhibitor and thrombin-activatable fibrinolysis inhibitor. IBD has also shown an inhibitory effect on the production of anticoagulants, such as antithrombin III, protein C, and protein S [16]. Further, chronic inflammation in IBD is presumed to induce vascular endothelial surfaces into a procoagulant state via cytokines (interleukin [IL] 1, tumor necrosis factor [TNF] α) and endotoxins [10]. Finally, pathogenic mechanisms unrelated to disease activity status include thrombocytosis, hyperactivity of platelets secondary to chronic inflammatory response, and increased CD40 ligand production by platelets [16]. The interaction between CD40-CD40L and cytokines (IL-1 and TNF-α) is known to increase the production of various cell adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and platelet endothelial cell adhesion molecule [10].

We believe that the untreated severe anemia in our patient is a major potentiating factor for thrombosis. Anemia has long been considered a thrombogenic factor [7] and a frequent complication of IBD [23]. We performed a literature review search using PubMed and Google Scholar for English-language articles from 2006 to 2020, using the key terms "cerebral venous thrombosis", "anemia", and "iron deficiency anemia". The main exclusion criteria used were (1) lack of anemia, (2) lack of CVT, (3) lack of CVT on neuroimaging, and (4) articles lacking sufficient data. The patient demographic data, clinical features, location of the CVT, diagnostic neuroimaging, and types of anemia are outlined in **Table 4**, which summarizes 21 case reports and 1 case series discussing 22 patients. Additionally, there are 5 case-control studies including a total of 222 patients and 1 cohort study of 51 patients. We also included 1 review of literature with 30 patients (with overlap of 1 case report in our table) that primarily focuses on abnormal prothrombotic laboratory findings [24].

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Table 4. Review of literature: Cases with cerebral venous thrombosis and anemia.

Article	Study type	Age/ gender	Initial Clinical Features	Location of CVT	Diagnostic imaging	Anemia type
Kinoshita 2006	Case report	14 M, 47 M	1. Headache and nausea 2. Worsening hemiparesis and seizures	1. End of the superior sagittal sinus to the left transverse sinus 2. Superior Sagittal Sinus	CTV	IDA
Ciurea 2006	Case report	22 F	Headache, vomiting, seizures	Left sigmoid sinus thrombosis	MRI, MRV	SCD
Balci 2007	Case report	38 F, 18 F	1. Headache, nausea, vomiting, hemiplegia 2. Headache, nausea, vomiting	1. Internal cerebral vein, vein of Galen, inferior sagittal and transverse sinus 2. Vein of Galen, vein of Rosenthal, straight and left transverse sinus	MRI, MRV, MRA	IDA
Ogata 2008	Case report	55 M	Seizures, hemiparesis	Superior Sagittal Sinus	CT, MRV, Angiography	IDA
Nicastro 2012	Case report	63 F	Headache, hemiplegia, global aphasia	Superior sagittal, transverse sinus	CT, MRI	IDA
Busani 2012	Case report	28 F	Headache, hemiplegia, global aphasia	Left transverse sinus	CT, MRI, MRV	IDA
Lee 2013	Case report	55 M	Headache, nausea, dizziness	Lateral sinus thrombosis	MRI	IDA
Yakota 2014	Case report	37 F	Aphasia, right sided weakness	Superior sagittal sinus	CVA	IDA
Zhu 2014	Case report	43 F	Recurrent seizures, progressive headache	Left transverse and sigmoid sinus	MRI	IDA
Shindo 2014	Case series	18-81 yo (13 F, 9 M pts)	Headache, impaired consciousness, seizures, focal motor deficit, ataxia	Superior Sagittal Sinus, transverse sinus, straight sinus	MRI	IDA
Nishioka 2014	Case report	47 F	Seizures, headache	Superior Sagittal Sinus, transverse sinus	MRI, angiography	IDA
Ignacio 2015	Case report	35 M	Headache, seizures	Superior Sagittal sinus	MRI	IDA
Jeong 2015	Case report	51 F	Headache, paresthesia	Superior Sagittal Sinus	CT, MRI	IDA
Nishida 2016	Case report	28 F	Altered mental status, vomiting	Straight sinus, great cerebral and deep middle cerebral vein	CT, MRI, MRV	IDA
Boon 2016	Case report	18 M	Headache, photophobia, nausea, vomiting	Left sigmoid and transverse sinus, jugular bulb	CT, CTV	IDA
Liang 2016	Case control	20-40 F (43 pts)	Headache, seizures, limb weakness, nausea, vomiting, distrubed consciousness, blurred vision, fever	Superior sagittal sinus, transverse sinus, sigmoid sinus, straight/inferior sinus, vein of Galen	CT, MRI, MRV, MRA	IDA
Thammishetti 2016	Case control	19-30 (44 F, 36 M pt)	Headache, papilledema, seizures, neurological deficit, hemiparesis, vomiting, visual disturbance	Superior Sagittal Sinus, transverse/sigmoid/petrosal/ straight sinuses	CTV, MRV	Anemia (IDA, normocytic, macrocytic)

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Table 4 continued. Review of literature: Cases with cerebral venous thrombosis and anemia.

Article	Study type	Age/ gender	Initial Clinical Features	Location of CVT	Diagnostic imaging	Anemia type
Krajickova 2016	Cohort study	18-76 (37 F, 14 M pts)	Impaired consciousness, focal deficits, seizures	Superior Sagittal Sinus, straight/transverse/sigmoid, deep cortical veins	MRI, MRV	Anemia
Takemaru 2017	Case control	25-81 (13 M, 3 F pts)	Headache, nausea, vomiting, seizure, coma, hemiparesis, speech/visual disturbance	Superior Sagittal Sinus, lateral sinus, straight sinus	CT, MRI, MRV	IDA
Kamel 2017	Case report	43 F	Headache, bilateral papilledema	Right transverse and sigmoid sinus, right internal jugular vein	MRV	IDA
Gao 2018	Case report	44 F	Headache, unilateral limb weakness	Superior Sagittal Sinus	CT, CTV	Aplastic
Kapur 2019	Case report	32 M	Headache, vomiting, ataxia, unilateral weakness, seizures	Right transverse and sigmoid sinus	MRI, MRV	Megaloblastic
Almussalam 2019	Case report	18 M	Right sided weakness	Deep Cerebral Venous Thrombosis and vein of Labbe	CT, MRV, Angiography	SCD
Menon 2019	Case report	43 F, 22 F	1. Headache, unilateral weakness 2. Headache, vomiting	1. Internal cerebral vein, vein of Galen and cortical vein 2. Superior sagittal and straight sinus, vein of Galen and deep cerebral vein	MRI, MRV	1. IDA; 2. No anemia
Bibi 2019	Case report	63 F	Headache, nausea, vomiting, confusion, hemiparesis	Left transverse and sigmoid sinus	CT, CTV	IDA
Algaidi 2020	Case control	37-39 (39 F, 16 M pts)	Headache, nausea, vomiting, altered consciousness, seizures, focal neurological deficits, visual defect, papilledema, altered behavior	Superior Sagittal Sinus, transverse sinus, sigmoid sinus, straight sinus, vein of Galen	CTV, MRV	IDA
Alhosan 2020	Case report and review	40 F	Diarrhea, headache, Altered Mental status, Hemiplegia	Left transverse and sigmoid sinuses, left jugular vein	CT, MRA, MRV	IDA, megaloblastic
Pathak 2020	Case control	21-40 (16 F, 12 M pts)	Headache, nausea, vomiting, blurred vision, altered sensorium, fever, seizures, focal neurological signs	Superior Sagittal Sinus, transverse sinus, sigmoid sinus, straight sinus	MRI	IDA
Komro 2020	Review of literature	19-65 (16 M, 14 F pts)	Headache, GI disturbance, seizures, focal neurological deficits, visual disturbance, altered mental status, papilledema	–	CT, CTV, MRI	Anemia

pts – patients; M – Male; F – Female; IDA – iron deficiency anemia; SCD – sickle cell disease; CT – computed tomography; MRI – magnetic resonance imaging; CTV – computed tomography venography; MRV – magnetic resonance venography; MRA – magnetic resonance angiography; CTA – computed tomography angiography.

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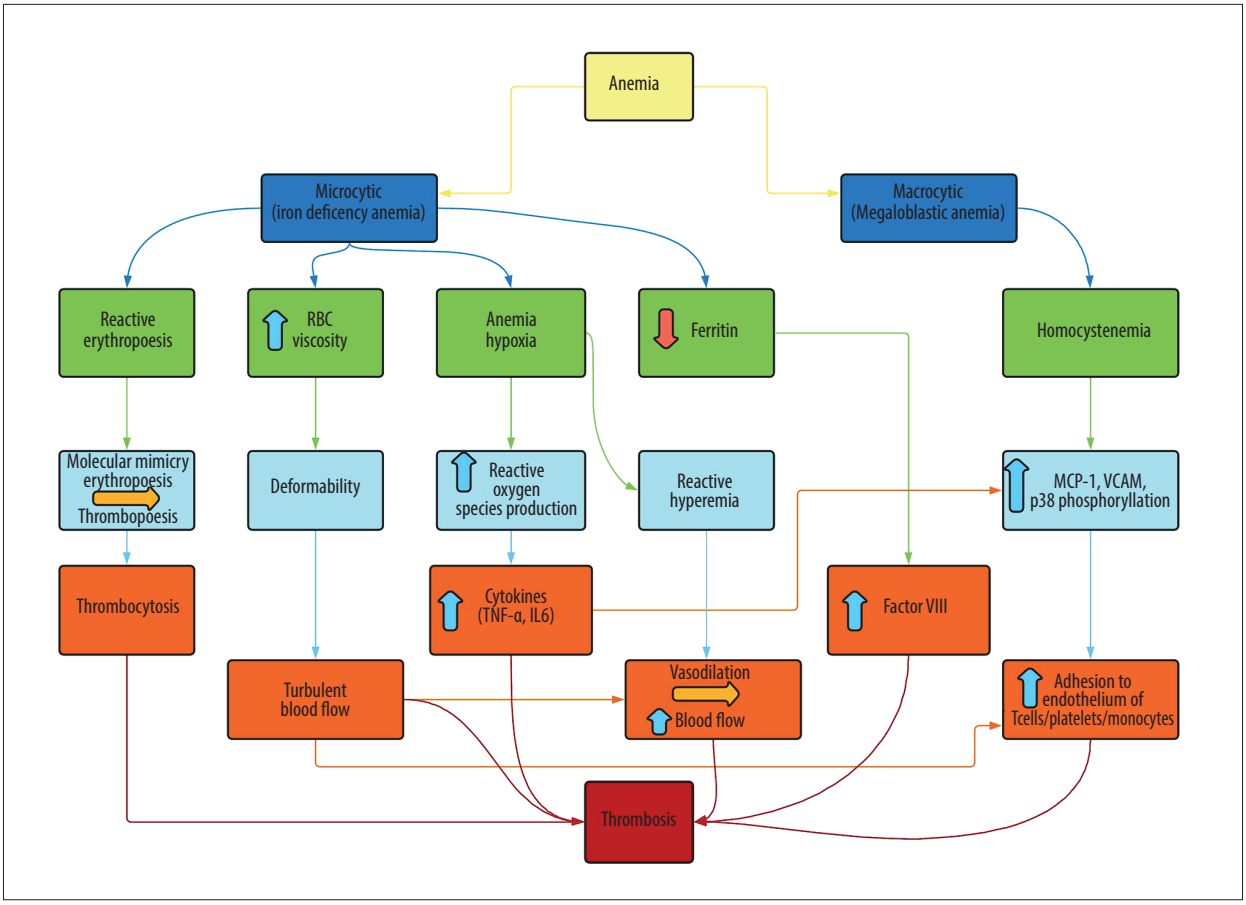

Figure 9. Flow chart: Pathogenesis of anemia causing thrombosis. MCP-1 – monocyte chemoattractant protein-1; RBC – red blood cell; TNF-α – tumor necrosis factor α; IL-6 – interleukin-6; VCAM – vascular cell adhesion molecule.

The International Study on Cerebral Vein and Dural Sinus Thrombosis found the correlation of anemia with CVT to be 9.2% [6], which was confirmed by Stolz et al for severe anemia (Hb <9 g/dL; 11.7% of cases, odds ratio [OR] 1.10) [8]. A stronger association between CVT and anemia (27% of cases, OR 4.4%) was later established by Coutinho et al in 2015 [11]. This pivotal relationship has recently been proven again in a large retrospective study of 6 million patients that identified 36,327 patients with iron deficiency anemia [25]. The risk of thrombosis in patients with iron deficiency anemia without thrombocytosis was 7.8%, which increased to 15.8% in patients with iron deficiency anemia and thrombocytosis [25].

Both microcytic and macrocytic anemias have been implicated as a cause of CVT in patients with IBD [11]. In patients with UC, there is a higher prevalence of iron deficiency anemia than of macrocytic anemia, both of which occur secondary to hematochezia, malabsorption, and chronic disease activity status [26]. The pathogenesis for CVT in microcytic anemia comprises 4 pathways: (1) reactive thrombocytosis due to molecular mimicry, (2) alteration in erythrocyte viscosity causing turbulent blood flow, (3) anemic hypoxia resulting in increased production of cytokines, and (4) low serum ferritin leading to increase production of factor VIII [9,27] (**Figure 9**). Macrocytic anemia, because of vitamin B_{12} and folate malabsorption in IBD, leads to homocysteinemia, an established risk factor for CVT [11,22]. Coutinho et al reported that 1.4% of patients (OR 8.9) with CVT had macrocytic anemia [11]. Homocysteine has been shown to increase endothelial inflammation by increasing production of monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1 as well as phosphorylation of p38. These changes cause an additional number of T cells and monocytes to adhere to the endothelium [16] (**Figure 9**). We encourage physicians to be aware of the fact that anemia has been strongly advocated as a prothrombotic factor, as it is seemingly overlooked in the clinical setting. Additionally, the interplay between the thrombogenic nature of IBD and anemia in the pathogenesis of CVT is important to acknowledge.

An average delay of 7 days in diagnosis of CVT can occur owing to a myriad of nonspecific clinical symptoms, although establishing the diagnosis may take up to several weeks [6]. The most common presentation is headache (90%) [1], which can progress over time and characteristically presents as a

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diffuse, severe pressure-type headache or a thunderclap headache [28-30]. The headache can be accompanied by other neurological features such as vomiting (29.2%), altered mental status (21.5%), papilledema (7.1%) [19], or diplopia following sixth nerve palsy [1], secondary to an increase in intracranial pressure (false localizing sign). Focal neurological deficits as a consequence of venous infarcts were seen in approximately 53% of patients [3,6,8,11,29], and focal or generalized seizures can occur in up to 40% of patients [1,2].

The aforementioned diverse presentation makes the diagnosis of CVT challenging, particularly when headache is the only presenting symptom. A diagnosis of CVT should be considered in young adults with IBD who present with a new-onset headache [18,31,32]. Initial workup including a complete blood count, basic metabolic panel, coagulation screen (bleeding time, prothrombin time, activated partial thromboplastin time), liver function tests, and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) should be followed by a D-dimer level, a hypercoagulability panel, and neurovascular imaging.

The use of D-dimer as a predictor of CVT was initially proposed by the European Stroke Organization in 2017 and has been endorsed by the European Academy of Neurology [32]. This is supported by the fact that D-dimer has a sensitivity of 97.8%, specificity of 84.9%, and negative predictive value of 99.8% for CVT [33]. A limitation to this suggestion, as raised by the European Stroke Organization, is that the reliability of D-dimer varies with time (symptoms lasting >1 week), thrombus load (number of sinuses involved), and clinical presentation [32]. D-dimer sensitivity decreases to 87.1%, especially in the presence of isolated headache [32-34]. Heldner et al recently introduced a new clinical scoring system (**Tables 5, 6**), based on D-dimer levels and risk stratification, for the pursuance of neurovascular imaging in CVT diagnosis [29].

Estimating the probability of CVT using this scoring system is based on individually weighted criteria (**Table 5**). The calculated score, in conjunction with D-dimer levels, yields different probabilities of CVT (low, moderate, high) (**Table 6**). D-dimer showed an effective exclusion of CVT when patients presented with low clinical probability (0-2 points) and D-dimer <500 ug/L. Moderate probability (3-5 points) and high probability (6-12 points) scores are associated with a lower reliability of D-dimer, and clinicians should pursue neurovascular imaging to diagnose CVT, irrespective of D-dimer levels.

Additionally, in this clinical score, thrombophilia has been defined as any hematological disorder related to coagulopathy [29]. Although the association between anemia and thrombosis is well established [6,8,11,25], it is underrecognized in clinical practice. Hence, taking anemia (thrombophilia) and the duration of symptoms (> 6 days) into account, our patient had a CVT clinical score of 6, indicating high probability. Thus, in our patient, this should have prompted further neuroimaging on the first ED visit, potentially avoiding the missed diagnosis and progression to further complications.

Table 5. Clinical scoring based on presentation [modified with permission from Heldner, 2020].

Criteria	Points
Seizure (s)	4
Thrombophilia (any hematological disorder)	4
Oral contraception	2
Duration of symptoms >6 days	2
Worst headache ever	1
Focal neurological deficits	1

A diagnosis of CVT is best confirmed by CT venography or MR venography [1,32]. Non-contrast head CT has a low sensitivity in diagnosing CVT (30%), but can be utilized to recognize complications of CVT [1]. Infrequent signs seen on non-contrast head CT include the dense triangle/dense clot sign and the cord sign [2,35,36]. The classic finding of empty delta sign on contrast-enhanced head CT has low sensitivity [1]. Contrast-enhanced and 2-dimensional time-of-flight MR venography are helpful in detecting well-established criterion standard noninvasive diagnostic tests for detecting CVT. They have high sensitivity in detecting CVT during the acute, subacute, and chronic phases. CT venography has a 95% sensitivity [37]. When CT venography or MR venography findings are inconclusive, cerebral angiography is needed to confirm the diagnosis of CVT [35,38,39]. Digital subtraction angiography can indicate intraluminal-filling defects, signs of venous congestion, and absence of cortical veins or dural sinuses [39].

The acute treatment of CVT involves anticoagulation with therapeutic doses of low-molecular-weight heparin or unfractionated heparin [1,22,40]. The risks and benefits of either option should be weighed and applied individually. The criterion standard, long-term treatment of CVT is warfarin, with a target INR of 2.0-3.0 [1,40]. In patients with IBD-induced CVT, transient hypercoagulability requires 3 months of anticoagulation treatment. In patients with an isolated episode of idiopathic CVT, 6 to 12 months of treatment is required. Recurrent episodes of CVT (2.2% with treatment) [41] or anticoagulant deficiency necessitate indefinite treatment [19]. Direct oral anticoagulants have been increasingly used as an alternative to warfarin for the chronic management of CVT because they show a comparable efficacy and an improved safety profile [42].

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Table 6. Probability groups and D-dimer levels [modified with permission from Heldner, 2020].

Cut-off (ug/l)	Sensitivity	Specificity	Negative predictive value
Low probability (0-2 points) and >500 ug/l	100.0	67.4	100.0
Moderate probability (3-5 points) and >500 ug/l	85.3	64.0	91.7
High probability (6-12 points) and >500 ug/l	89.8	75.0	37.5

ug/L – microgram/liter.

The indications for endovascular intervention include clinical deterioration despite anticoagulation, progressive/severe neurological deficits, seizures, stupor, posterior fossa/deep-cerebral venous system involvement, and coma and patients who have contraindications to anticoagulation therapy [39]. A combination of interventional techniques, including local thrombolysis, direct aspiration thrombectomy, stent retriever thrombectomy, balloon thrombectomy, balloon angioplasty, stenting, and rheolytic thrombectomy, may be required for revascularization [39]. The Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis randomized control trial further suggests that neurointervention may not improve functional outcomes of patients with CVT, as compared with standard clinical care [43]. There are currently no consensus guidelines for these interventional procedures [39]. Invasive interventions, including decompressive craniectomy and hematoma evacuation, should be reserved for patients with intractable intracranial hypertension or large parenchymal lesions leading to herniation [39].

Early neurological complications of CVT include hemorrhagic strokes (40%), intracranial hypertension (40%), communicating hydrocephalus (6.6%), and status epilepticus [1]. Late complications include chronic headaches, which should be evaluated for recurring CVT, seizures (5-32%), vision loss (2-4%), and dural arteriovenous fistula formation (1-3%), secondary to persistent occlusion [1]. Saposnik et al showed that with appropriate treatment, 79% of patients have complete recovery, while 10.4% experience persistent mild to moderate disability (modified Rankin Scale [mRS] score 2-3), and 2.2% have severe disability (mRS score 4-5) [1]. It is imperative to note that the overall mortality rate for CVT alone is 5.6% to 9.4% [36]; however, CVT in conjunction with UC, has a mortality rate as high as 25% [6].

Conclusions

Cerebral venous thrombosis should be investigated in patients with IBD who report new-onset or worsening headaches, especially in the context of underlying anemia. Diagnosing CVT can be challenging owing to a nonspecific clinical presentation and lack of diagnostic laboratory markers. Establishing a timely diagnosis of CVT is critical in patients with IBD, given the high mortality rate. The current American Heart Association/American Stroke Association (AHA/ASA) update regarding the diagnosis and management of CVT was published in 2011 [1]. Heldner et al [29] recently developed a clinical probability score to guide in the pursuance of diagnostic neurovascular imaging. This score can better assist in the risk stratification of patients presenting to a clinician, especially in the acute setting, analogous to the Wells' criteria for deep vein thrombosis and pulmonary embolism. We endorse implementing the CVT clinical probability score in future AHA/ASA recommendations for CVT diagnosis. Additionally, clinicians should be aware that anemia is a major risk factor for CVT in patients with UC.

Acknowledgements

We would like to thank Sravya Kattula, PhD for her expertise and assistance throughout all aspects of our study and for her help in writing the manuscript.

Conflicts of Interest

None.

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