

A review of the literature on three extraintestinal complications of ulcerative colitis: an ulcerative colitis flare complicated by Budd-Chiari syndrome, cerebral venous thrombosis and idiopathic thrombocytopenia

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Abstract

Extraintestinal manifestations are well described and recognized in association with ulcerative colitis. Immunologically mediated and thrombotic events are among the more rare manifestations associated with flares. These manifestations include Budd-Chiari syndrome, idiopathic thrombocytopenia, and cerebral venous thrombosis. A 22-year-old male with a three-year history of ulcerative colitis presented with worsening hematochezia, fatigue, headache and upper respiratory symptoms. Laboratory evaluation demonstrated a platelet count of $24 \times 10^9/L$ (normal baseline platelet count noted 3 months prior) and hemoglobin of $8.6 \times 10^9/L$. Imaging demonstrated hepatic venous thrombosis consistent with Budd-Chiari syndrome and cerebral venous thrombosis. Based on peripheral smear analysis and eventual marked response to steroids, a diagnosis of idiopathic thrombocytopenia was made. He was started on prednisone 40mg daily with brisk improvement in both his ulcerative colitis flare and his platelet count increasing above $100 \times 10^9/L$. He was therapeutically anticoagulated for the cerebral venous thrombosis. He continued to do well and was discharged on therapeutic enoxaparin and a 40 mg prednisone taper without recurrent flare or idiopathic thrombocytopenia two weeks post-hospitalization. To our knowledge, this is the first report of all three known but rare complications diagnosed concurrently in the same patient. This review examines three extraintestinal complications of ulcerative colitis, including the presentation, diagnosis, and treatment. (*Acta gastroenterol. belg.*, 2013, 76, 311-316).

Key words: ulcerative colitis, idiopathic thrombocytopenia, ITP, Budd-Chiari syndrome, BCS, cerebral venous thrombosis, CVT, extraintestinal complications, complications.

Introduction

Ulcerative Colitis (UC) has been associated with many extraintestinal manifestations. Budd-Chiari syndrome (BCS), cerebral venous thrombosis (CVT) and Idiopathic thrombocytopenia (ITP) have all been described as rare complications in patients with UC (1-8). However, to our knowledge, this is the first report of all three complications occurring simultaneously during a UC flare. Treatment of UC complications during a flare may be complicated by active hematochezia.

Case report

A 22-year-old male with a three-year history of UC presented with increased bowel frequency, hematochezia, and flu-like symptoms. He was originally diagnosed with left sided colitis which had historically been well controlled with sulfasalazine and occasional rectal ste-

roid therapy. However, his last surveillance colonoscopy six months prior to evaluation demonstrated mild chronic pancolitis. At presentation he was on 6-mercaptopurine (6-MP) and prednisone 20 mg daily for a flare that began two months prior. He was well controlled on steroids until three days prior to admission when he began having 4-5 bloody, liquid bowel movements per day, dyspnea on exertion, and seven days of upper respiratory symptoms, including a productive cough, sore throat, nasal congestion, headache, and subjective fevers.

Initial vital signs were unremarkable, including blood pressure of 117/67, heart rate of 70, respiratory rate of 16, temperature of 98.3F, and oxygen saturation 100% on room air. Examination revealed conjunctival and mucosal pallor but he was in no acute distress. Abdominal examination revealed normoactive bowel sounds without tenderness to palpation, rebound, guarding or organomegaly. There were no stigmata of chronic liver disease.

Initial laboratory evaluation (Table 1) revealed hemoglobin of 8.6 g/dL, white blood cell count of $5.0 \times 10^9/L$ with a granulocytic predominance of 89%, and a platelet count of $25 \times 10^9/L$. A peripheral smear showed giant platelets without clumping or schistocytes. Prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), d-dimer and lactate dehydrogenase were elevated. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were markedly elevated. Fibrinogen was decreased and haptoglobin, alkaline phosphatase (ALP), and total bilirubin were all within normal limits.

Stool testing was positive for fecal leukocytes with numerous polymorphoneutrophils but the stool culture was negative (*Salmonella*, *Shigella*, *Edwardsiella*, *Campylobacter*, *Plesiomonas*, *Aeromonas*, *Yersinia*, *Vibrio*, *Enterococcus*, and *Ecoli* 0157), ova and parasite testing was negative, and evaluation was negative for *Clostridium difficile* toxin B DNA. Hepatitis A, B, and C, EBV, CMV, HSV 1+2, ceruloplasmin, anti-neutrophil

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Table 1. — Admission Laboratory Values

Laboratory Test	Result	Reference Range
Prothrombin time (PT)	20.2	11.7-14.2 sec
Partial thromboplastin time (PTT)	40	24-36 sec
International normalized ratio (INR)	1.8	0.8-1.3
Fibrinogen	177	196-468 mg/dL
Fibrin D-dimer	18.47	< 0.60 mcg/mL
Lactate dehydrogenase	5190	313-618 Units/L
Haptoglobin	219	30-200 mg/dL
Alanine aminotransferase	1235	13-69 Units/L
Aspartate aminotransferase	1412	15-46 Units/L
Alkaline phosphatase	104	38-126 Units/L
Total bilirubin	0.9	.1-1.3 mg/dL

antibody screen, anti-smooth muscle antibodies, urine drug screen, acetaminophen, and salicylate screening were all negative.

He was admitted with a UC flare complicated by symptomatic anemia secondary to hematochezia. Piperacillin-tazobactam was empirically started and his prednisone was increased from 20 to 40 mg orally daily. He was transfused one unit of packed red blood cells, two units of fresh frozen plasma, and given 10 mg of subcutaneous vitamin K. Although he had a previously normal baseline thiopurine methyltransferase (TPMT) level, his 6-MP was held due to concern for potential hepatic toxicity, while awaiting 6-MP levels. TPMT genotype analysis was performed and eventually resulted as negative for heterozygous mutations.

A right upper quadrant ultrasound with Doppler, followed by an abdominal computed tomography (CT) with contrast, demonstrated gallbladder wall thickening without cholelithiasis and partial thrombosis of right, medial, and left hepatic veins consistent with BCS (Figs. 1-3). Due to the active hematochezia and non-obstructive hepatic vein thrombosis, anticoagulation was deferred. The patient complained of a persistent headache and a head CT without contrast was obtained, which demonstrated no acute intracranial pathology, but did reveal multiple intracranial calcifications. Subsequent magnetic resonance imaging (MRI) of the head with and without gadolinium revealed a superior sagittal sinus thrombosis. Asymmetric serpiginous hypointense signals in several cortical veins suspicious for thromboses were also noted.

After consultation with gastroenterology, hematology, and neurology, the patient was started on therapeutic anticoagulation with enoxaparin 1 mg/kg subcutaneous twice daily. Hematology also recommended warfarin for at least six months. He continued to rapidly improve on prednisone with resolution of his UC flare, his aminotransferases and INR normalizing, and his platelet count increasing to $222 \times 10^9/L$ by day three of admission. Although 6-MP can cause myelosuppression independent of TPMT deficiency or a heterozygous mutation, given the appearance of the peripheral smear and the brisk re-

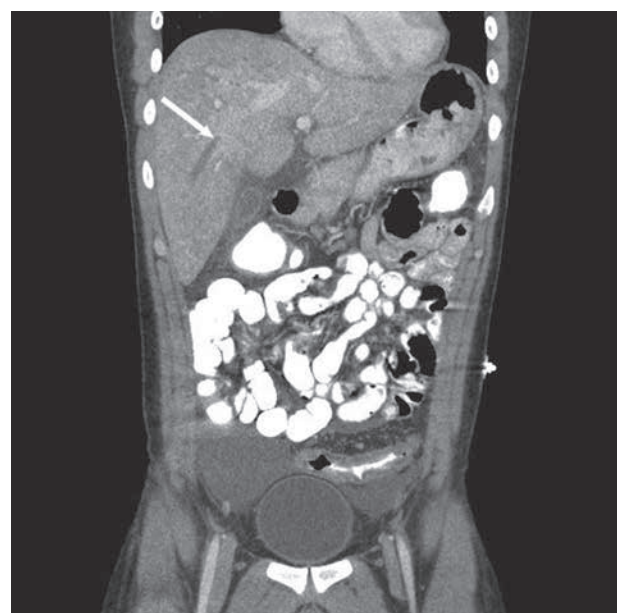


Fig. 1. — Computed tomography demonstrates hypoattenuating foci within segments of the middle and right hepatic veins.

sponse to steroids, his thrombocytopenia was consistent with ITP. However, resolution of myelosuppression often occurs following discontinuation of 6-MP, and this possibility cannot be completely excluded.

An extensive hypercoagulability evaluation revealed an antithrombin III deficiency with a level of 61.0% (80-150%). Of note, low molecular weight or unfractionated heparin can result in a low antithrombin III activity; however, he was not on heparin when this lab was obtained. Multiple antithrombin III levels were obtained three months after discharge and were normal at 112 to 146%, which is consistent with an acquired deficiency secondary to gastrointestinal loss and/or intravascular consumption. Further workup with Russell Viper Venom Clotting Time, anticardiolipin antibody, B2-glycoprotein, Factor V Leiden, protein C&S activity, and prothrombin was negative.



Fig. 2. — Computed tomography demonstrates a single focus of thrombus in a segment of the left hepatic vein.

The patient was discharged on therapeutic enoxaparin and prednisone at 40 mg daily. At two weeks post-hospitalization he was symptom free and his platelet count was $390 \times 10^9/L$. Approximately three weeks after discharge, he was restarted on 6-MP with continued prednisone taper and over six months of follow up had no further symptoms or complications.

Discussion

Ulcerative Colitis and Budd-Chiari Syndrome

UC is associated with increased risk for both arterial and venous thrombotic events (9,10). During a UC flare the risk for thrombosis is up to eight times higher (11). Events during a flare which predispose to thrombosis include increased cytokines and inflammatory mediators (e.g. IL-1, IL-6, TNF- α) that interact with coagulation cascades (12). A flare may also increase intestinal epithelial permeability, resulting in bacterial translocation with endotoxemia and activation of the coagulation cascade (13). Another factor increasing coagulation may be the ability of inflammatory cytokines to counteract inherent anticoagulation activity (14).

The most common risk factors for developing venous thromboembolism (VTE) in UC are coexisting hypercoagulabilities including factor V Leiden mutations, antiphospholipid antibody syndrome, and hyperhomocysteinemia (15). The most common VTEs are deep vein thrombosis (DVT) and pulmonary embolism (PE). The risk for VTE persists even after procolectomy, suggesting a systemic rather than local inflammatory etiology (16).

BCS is a condition that results from hepatic venous outflow tract obstruction. It is most commonly associated

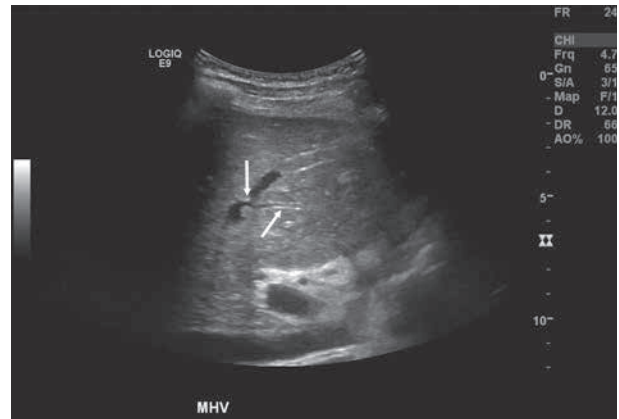


Fig. 3. — Ultrasound demonstrates a thrombus within the medial hepatic vein and right hepatic vein. The left hepatic vein was poorly visualized.

with predisposing conditions such as myeloproliferative disorders (usually polycythemia vera), hypercoagulabilities, or malignancies (17). It is a rare extra-intestinal complication of UC and the first described case of co-existing UC and BCS was in 1945 on necropsy (1). The incidence of UC and BCS was reported as 39% on one necropsy study (18). The first report of BCS diagnosed in a living patient was in 1988 by Brinson *et al.* (2). Of the 16 published cases reviewable on PubMed of UC associated with BCS, only six reports were diagnosed in living adult patients and the remainder on necropsy (19). Four of the six living patients had a coexisting hypercoagulability disorder (two polycythemia vera, one antiphospholipid antibody syndrome, and one MTHFR mutation) and a fifth was not tested. A recent report described a patient with UC, BCS, and no coexisting hypercoagulability disorder (19). This last case was positive for *Clostridium difficile* enterocolitis, which was postulated as a potential pro-inflammatory mediator of the coagulation cascade predisposing to BCS.

The diagnosis of BCS is suspected in patients with abdominal pain, ascites, and hepatomegaly. It is defined as a disruption of the hepatic outflow, either intravascular (thrombosis) or extravascular (compression) disruption. Classic BCS is considered to be primary hepatic vein thrombosis versus thrombosis of the hepatic portion of the inferior vena cava (IVC). A proposal in 1998 recommended differentiating primary hepatic vein thrombosis as BCS and IVC thrombosis as “obliterative hepatocavopathy” (20).

Diagnosis is confirmed on imaging. Although hepatic venography is the gold standard, it is invasive and usually reserved for when non-invasive studies are non-diagnostic or prior to intervention. Doppler ultrasound and computed tomography are frequently used to diagnose BCS and although a few studies demonstrated magnetic resonance angiography to be more precise in defining the location of the obstruction, there is no consensus on when to use one or the other (21,22).

Laboratory abnormalities often include elevated aminotransferases. AST and ALT levels are often between 100 to greater than 600 units/L ; elevations greater than five times the upper limit of normal have been found to correlate with acute and severe BCS²³. ALP is often between 300-400 unit/L and serum bilirubin is usually < 10 mg/dL.

Treatment guidelines have been established by the American Association for the Study of Liver Diseases (AASLD) in 2009 and recommend life-long anticoagulation unless contraindicated. Extensive testing for a hypercoagulability disorder should be performed. If the patients are symptomatic, percutaneous venography may be helpful to define the location of the obstruction, evaluate for venous obstruction and if necessary stents may be placed. Transjugular intrahepatic portosystemic shunt (TIPS) is an option in the case of medical failure with anticoagulation. Liver transplant is reserved for fulminate liver failure or patients who do not respond to TIPS.

As discussed above, thrombotic complications in UC are more likely to occur during an active flare. Significant hematochezia often experienced during a flare complicates the recommended treatment of anticoagulation.

Ulcerative Colitis and Cerebral Venous Thrombosis

CVT is a known complication of inflammatory bowel disease (IBD). The incidence of CVT in IBD is reported to range from 1.3 to 7.5% annually (3). It is reportedly more common in UC than in CD (24). Most patients with UC and CVT have an inherited or acquired hypercoagulability. However, other possible etiologies include concurrent cancer, head trauma, hematologic conditions resulting in hyperviscosity, drugs, sepsis, central nervous system infection, protein C and S deficiency, pregnancy, and antithrombin III deficiency (25). IBD is associated with decreased antithrombin III through intravascular consumption and gastrointestinal loss, increased fibrinogen, increased factors V and VIII, and thrombocytosis (26,27). Although cerebral thrombotic events are more common during UC flares, there are documented cases of CVT occurring during remission (28,29). There is also a case of CVT occurring 10 years after colectomy of UC (30).

Headache is the most frequent symptom ; it is often severe and diffuse and may herald the onset of a neurological deficit (31). Although the signs and symptoms are variable and may include headache, seizure, and altered mental status, any neurological deficit in a patient with UC should prompt evaluation for CVT (31). MRI with venography or CT venography with multislice units are likely equally sensitive for the diagnosis of venous sinus occlusion (31). Angiography is generally not necessary and is reserved for equivocal diagnosis.

Five percent of patients with CVT die in the acute phase (32). The consensus is treatment with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) (33). According to the American

Academy of Chest Physicians guidelines for ischemic stroke, anticoagulation is recommended and either LMWH or UFH can be used as the initial treatment, even in the context of a hemorrhage within the venous infarction³⁴. Once the patient is stable, one should be transitioned to oral anticoagulation for three to six months (34). However, if there is an underlying hypercoagulability, anticoagulation may continue indefinitely. For severe and rapid neurological deterioration, consider thrombolytics (25,35-41). Close guidance from neurosurgery and hematology colleagues is crucial.

Treatment of CVT during an UC flare is complicated by the potential for exacerbating lower gastrointestinal bleeding. If withholding anticoagulation could result in a potentially devastating neurologic insult, a total colectomy may be necessary for refractory bleeding.

Ulcerative Colitis and Idiopathic Thrombocytopenia

Various hematologic manifestations are associated with UC including anemia, thrombocytosis and leukocytosis. Thrombocytopenia and leukopenia are usually a side effect of immunosuppressive medications (42). Anemia is the most common and is usually secondary to blood loss and iron-deficiency anemia ; other causes of anemia may include vitamins B-12 and folate deficiencies from malabsorption, or anemia of chronic disease. ITP is a rare extra-intestinal complication of UC (5,7,8, 42,43).

It has been hypothesized that along with increased platelet destruction, antigenic mimicry is the etiology of ITP in UC (42). Specifically, it is presumed there are peptide sequences on the platelet surface that is similar to those of bacterial glycoproteins. Exposure to antigen-presenting cells to bacterial antigens occurs in the colonic mucosa and production of antibodies follows by stimulating antigen primed B-cells. The antibodies eventually cross-react with platelet antigens such as GPIIb/IIIa (44). This is supported by the finding that a UC flare almost always precedes ITP, ITP often resolves with resolution of the flare, and considering that colectomy is often curative for refractory ITP (8,43,45). It has also been demonstrated that the platelet-associated IgG (PAIgG) decreases with treatment of UC and ITP, either medically or surgically (45). However, there is a report of ITP developing after colectomy in a pediatric patient (46). There is also a report of ITP preceding the diagnosis of UC (47) ; however, it can be argued that subclinical UC with inflammation and resultant bacterial translocation may have been present in those patients.

Diagnosis of ITP in UC requires exclusion of other potential etiologies of secondary thrombocytopenia. Adverse drug reactions, disseminated intravascular coagulation (DIC), and viral infection are all common causes of secondary thrombocytopenia. Adverse drug reaction must be considered in UC patients treated with 5-ASA or azathioprine (48,49). Drug-induced thrombocytopenia often displays hypocellularity on bone marrow examination.

Examination of the peripheral smear should be performed to evaluate for schistocytes and platelet agglutination to rule out other causes of thrombocytopenia. In ITP, platelets should be normal to large in size. A meticulous drug history, including herbals and over-the-counter medications, should be obtained to evaluate for the many possible culprits of drug-induced thrombocytopenia (50). The American Society of Hematology currently does not recommend antiplatelet antibody evaluation for diagnosis or routine bone marrow biopsy (51,52). All patients with newly diagnosed ITP should be tested for HIV and HCV as ITP generally responds to treatment of the viral infection (52).

Treatment of ITP in UC involves primarily targeting control of UC ; ITP often resolves with improvement of the UC flare. Zlatanovic *et al.* reviewed 22 cases of inflammatory bowel disease complicated by ITP (3 Crohn's patients and 19 with UC). In this review, ITP frequently responded to steroids ; however, in cases refractory to steroids, higher doses of steroids, immunosuppressants (6-MP, cyclosporine), intravenous immunoglobulin (IVIG), or splenectomy were ultimately effective (42). Several reports of UC and ITP refractory to medical therapy and splenectomy demonstrated ultimate therapeutic success with colectomy (8,53,54). The most recent report of steroid and IVIG refractory UC complicated by ITP, in an adult, demonstrated for the first time that both conditions responded to therapy with infliximab (55).

Conclusion

Extraintestinal manifestations are well described and recognized in association with UC. One such entity is arterial and venous thrombosis, which occurs at a higher frequency during a UC flare. One of the least common thromboses is BCS and only six cases have been reported in living patients. Another uncommon thrombotic complication is CVT, often secondary to an acquired anti-thrombin III deficiency due to gastrointestinal loss and intravascular consumption. Immunologically mediated hematologic disease is also a rare entity associated with UC. In a majority of case reports the UC flare precedes or occurs concomitantly with the onset of ITP, which is suggestive of a causal relationship.

The treatment of BCS in a UC flare is complicated by active hematochezia ; however, non-obstructive thromboses do not require urgent treatment. Due to high morbidity and mortality, CVT requires anticoagulation, which may complicate the treatment of a UC flare, especially in steroid-refractory cases. ITP generally responds well to steroids ; however there are reports of steroid-refractory cases requiring colectomy, which was reported as a successful treatment for both UC and ITP.

Our case demonstrates a steroid responsive thrombocytopenia consistent with secondary ITP. Our patient was also diagnosed with BCS and CVT, which were successfully treated with anticoagulation in the context of a steroid-responsive UC flare. ITP, BCS, and CVT

have all been described as extraintestinal complications in patients with UC. However, to our knowledge, this is the first report of all three complications occurring simultaneously during a UC flare.

Disclosure statement

The authors have no disclosures and no conflicts of interest to declare.

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