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CASE REPORT

Budd-Chiari syndrome in a patient with ulcerative colitis and no inherited coagulopathy

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Abstract

We report a case of 27 year old female patient who was admitted to the hospital with an acute flare up of ulcerative colitis. The patient presented with complaints of persistent abdominal pain and bloody diarrhea despite aggressive therapy for her ulcerative colitis. A CT scan of the abdomen on admission revealed hepatic vein thrombosis, suggesting a diagnosis of Budd-Chiari syndrome. Significantly, an associated thrombosis of the inferior mesenteric vein was also detected. Based on imaging data and clinical assessment, the patient was started on anticoagulation therapy and an extensive work-up for hypercoagulability was initiated. Up to the time of publication, no significant findings suggesting this patient has an underlying coagulation disorder have been found. Based on our search of PUBMED, this report is one of only five reported adult cases of Budd-Chiari Syndrome associated with ulcerative colitis in the English literature in living patients without evidence of a co-existing coagulation disorder. This case highlights the potential for thrombosis at unusual sites in ulcerative colitis patients even in the absence of classical coagulation abnormalities. In addition to the case presented, we provide a brief review of previously reported cases of Budd-Chiari Syndrome occurring in patients with inflammatory bowel disease.

Key words: Ulcerative colitis; Inflammatory bowel disease; Budd-Chiari syndrome; Thrombosis; Coagulopathy

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INTRODUCTION

Patients with inflammatory bowel disease are at increased risk for thromboembolic complications. We present the case of a patient with ulcerative colitis (UC) complicated by the development of Budd-Chiari Syndrome (BCS) likely precipitated by an acute flare up of her UC. The incidence of venous thrombosis in UC was found to be 39% in one necropsy study[1], but hepatic vein thrombosis and BCS have been reported only as a rare extra intestinal complication of UC. Very few cases occurring in patients without an underlying coagulation disorder have been reported in the literature. In addition to the presentation of our patient, we review the literature describing the other reported cases and provide a brief clinical overview and outcome of all reported adult cases.

CASE REPORT

The patient was a 27 year old woman with a history of UC (pancolitis) diagnosed six months prior to admission. Her

disease was not well controlled despite aggressive management including treatment with certolizumab. The patient presented to the hospital after she had three episodes of bloody stools on the day of admission. She complained of diarrhea 12-15 times a day along with some abdominal pain for two days before admission. In addition, the patient stated she had decreased appetite and had lost six pounds in two months. She underwent a colonoscopy with biopsy six months prior to admission at the time of diagnosis of UC and no evidence of malignancy was detected. On admission, she denied any other symptoms, including fevers, chills, abdominal distention or mental status changes.

Physical exam on admission revealed an ill appearing woman with moderate pain but not in distress. She had a temperature of 98.7 F, a blood pressure of 96/60 mmHg (baseline for this patient), a pulse of 80 beats per minute (regular) and a respiratory rate of 16/min with an oxygen saturation of 99% on room air. Auscultation of the heart and lungs revealed no detectable abnormalities. Her abdomen was moderately tender to deep palpation but was not distended. Bowel sounds were present and there was an absence of rebound tenderness, rigidity or guarding. Her neurological examination was normal.

Pertinent labs on admission included hemoglobin of 9.2 gm/dL, a serum albumin of 2.3 gm/dL and liver enzymes within normal limits. On admission, mesalamine and Ⅳ steroids were started as initial therapy for the exacerbation of UC. A CT scan of abdomen was performed for intractable abdominal pain, which revealed hepatic vein thrombosis, supporting the diagnosis of BCS (Figure 1A); these findings were not present on a CT scan of the abdomen performed two months prior to admission (Figure 1B). She was therapeutically anticoagulated with enoxaparin as a bridge to warfarin therapy. The patient's stool collected on admission tested positive for clostridium difficile toxin on hospital day 3, which further complicated her inpatient management and she was started on oral vancomycin therapy. Fortunately, over the course of her stay in the hospital, the patient's clinical condition improved and she was discharged in good health.

Given this unusual presentation, a thorough investigation into other potential causes of this patient's hypercoagulability was performed which included a bone marrow biopsy to evaluate for myeloproliferative diseases, as well as laboratory studies to assess for the presence of paroxysmal nocturnal hemoglobulinuria, antiphospholipid antibody syndromes, deficiencies of natural anticoagulants (antithrombin Ⅲ, protein C and protein S), Factor Ⅴ Leiden mutation, prothrombin Ⅱ mutation, hyperhomocysteinemia, and a leukemia and lymphoma screen. No alternate etiology for the patient's apparent hypercoagulable state was identified. Of note, the patient was not on oral contraceptive medications on admission and for at least 7 mo prior to admission.

A follow up CT scan of the patient's abdomen two months later demonstrated a partial resolution of the hepatic vein thrombosis and her hepatic function remains normal (Figure 1C). She is currently in remission for her UC on Certolizumab and will continue on coumadin therapy indefinitely.

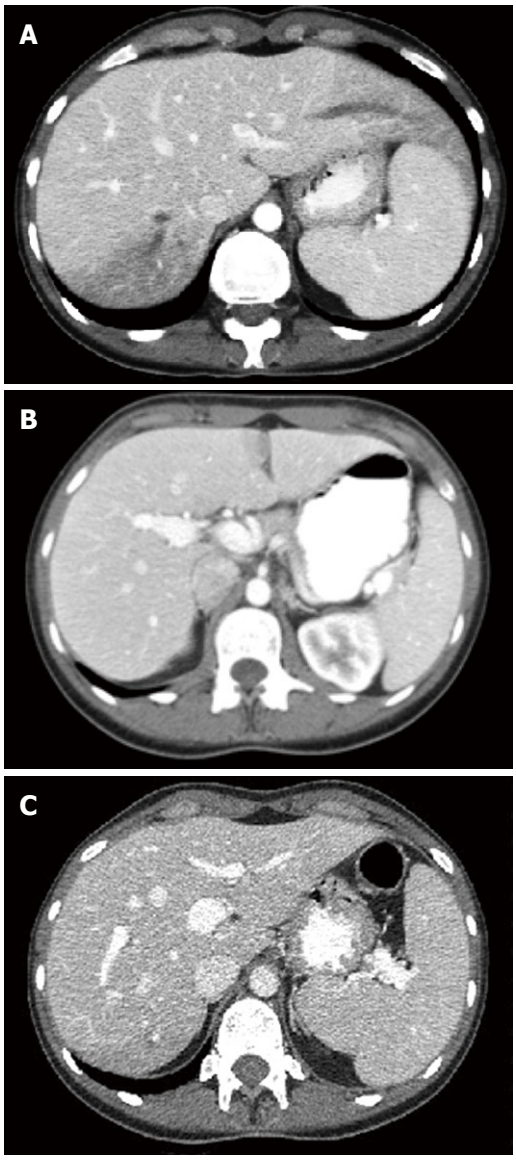

Figure 1 Abdominal computed tomography scans of patient at time points indicated. A: Abdominal computed tomography (CT) scan of the patient on admission demonstrates clear evidence of hepatic vein thrombosis; B: CT scan of the abdomen performed two months prior to admission revealed no evidence of hepatic vein thrombosis; C: Partial resolution of hepatic vein thrombosis two months after admission and initiation of anticoagulation.

DISCUSSION

BCS is characterized by venous congestion secondary to processes that interrupt or diminish the normal blood flow out of the liver[2]. Fatty changes, pericholangitis, sclerosing cholangitis and cirrhosis are well-recognized hepatic complications of UC but UC as a precipitant of BCS in the absence of other heritable causes has been only rarely reported. Patients with UC are at increased risk for venous thromboembolism at baseline but the risk is eight times higher during a flare up[3]. UC is also associated with an increased

risk of arterial thromboembolic events[4]. The incidence of venous thrombosis in UC was found to be 39% in necropsy studies[1], but hepatic vein thrombosis is a rare extra intestinal complication of UC. This case report is only one of five published reports of BCS diagnosed in living adult patients with IBD. In addition to our findings, we briefly summarize all 14 published BCS cases associated with UC and highlight features of the 12 reported cases published in English, with a focus on adult patients and those with co-exisiting inherited hypercoagulability.

The relative contribution of inherited thrombophilia to the development of VTE in patients with IBD remains unclear. Solem *et al* have found the rates of thrombophilic abnormalities among IBD patients in their cohort to be collectively similar to patients without IBD; however, the incidence of specific inherited coagulopathies was found to be individually uncommon[5]. Moreover, data from a case-control analysis published by Spina *et al*[3] suggest that classical inherited coagulation disorders are less frequent among IBD patients than age matched and VTE site-matched controls without IBD. Both of these studies have shown that the risk of VTE development among IBD patients is positively associated with both disease extent and activity (temporal association). Furthermore, as a whole, VTE in IBD patients occurs earlier in life than in those without IBD[6,7]. These and other findings support the classification of IBD as an independent risk factor for the development of VTE. However, as noted by previous authors, the acquisition of non-heritable risk factors for thromboembolic disease among IBD patients, particularly during acute flare ups is likely contributory. Although limited by its size, the study by Solem *et al* also found that UC patients remain at higher risk of venous thromboembolism even after a proctocolectomy, suggesting the systemic as opposed to the local origin of thrombophilia[5]. Taken together with other data, this suggests that VTE is a true extraintestinal manifestation of IBD.

More recent analyses have examined in greater depth whether consistent abnormalities in either the levels or functionality of components of the coagulation cascade can be detected in patients with IBD (reviewed in[8]). Various reports have demonstrated abnormalities in select haemostatic pathways in IBD patients including abnormalities of coagulation[9-13], platelet function[14-17], fibrinolysis[18-20] and endothelial function[21-23]. However, difficulties with intercomparison between studies and discordant results have made it challenging to draw firm conclusions. Furthermore, work over the past decade has elucidated functional links between both innate and adaptive immune function and coagulation cascades[24-26]. Indeed, IBD-associated alterations in the interaction between the immune system and coagulation pathways have been explored as a mechanism of VTE in these patients, as has the effect of nutritional deficiencies[8], which can be common in IBD patients. However, no single underlying abnormality in these interrelationships has been consistently linked to the development of VTE in IBD patients.

Although the precise mechanism responsible for increased risk of thromboembolism in patients with IBD remains obscure, several possible mechanisms have been hypothesized to contribute. While patients with IBD are predisposed to VTE even during remission, they appear to be particularly at risk for VTE during acute flare ups[27]. During an acute flare up of UC, increased systemic levels of various cytokines and other inflammatory mediators (e.g. IL-1, 1L-6 and TNF-alpha) can activate pro-inflammatory signaling in endothelial and immune cells and can modulate coagulation cascades predisposing patients to thrombosis[8]. Furthermore, Vassiliadis *et al* have proposed that increased intestinal epithelial permeability during an acute flare up facilitates bacterial translocation resulting in systemic endotoxinemia, which leads to a lowered threshold for activation of the coagulation cascade[28]. Notably, several groups have demonstrated that pro-inflammatory cytokines can counteract natural anticoagulant activity leading to a hypercoagulable state[29]. Rosenberg *et al* and Socha *et al* have suggested that loco-regional imbalances of endothelial cell-dependent procoagulant and anticoagulant activity underlies the thrombotic selectivity for some vessels such as the hepatic veins in cases of BCS[30,31]. However, given the low number of reported cases of BCS associated with IBD patients, the relevance of these putative mechanisms to cases such as that presented here is difficult to estimate. Our patient was found to have a concomitant *Clostridium difficile*-associated enterocolitis at presentation that we suggest could have caused additional regional proinflammatory signaling and coagulation dysfunction, possibly explaining the VTE in such a unique site leading to BCS.

We searched PUBMED and found 14 published cases of BCS coexisting with UC in the English literature (Table 1). One case was reported in German and another in Korean. Four of these reported patients were pediatric patients. Of these published reports, eight describe adult cases including four patients that were diagnosed based on necropsy studies. To our knowledge, our patient represents only the fifth reported case of coexisting BCS and UC reported in living adult patients. Excluding those diagnosed at necropsy, it is notable that three out of four of the previously reported patients had evidence of a coexisting coagulation disorder; two had polycythemia vera and one had antiphospholipid antibody syndrome, while the presence of a coexisiting coagulation disorder in the remaining patient was unknown at publication. Interestingly, among the 4 reported pediatric patients, only one was found to have a coexisting coagulation disorder upon work-up. A brief analysis of these patients demonstrates them to be predominantly female with BCS presenting or diagnosed during an acute exacerbation of UC. Importantly, those successfully diagnosed with BCS when alive survived the acute event in all cases.

Among reported adult patients, Kelsey *et al* first described a case of coexisting BCS and UC in 1945 during a necropsy study[32]. The next three reported cases were also from necropsy studies; one case by Jorgensen in 1958[33] and two cases by Chesner IM *et al* in 1986[34]. The first case of BCS and UC diagnosed in a living patient was reported

Table 1 Reported cases of Budd-Chiari Syndrome occurring in patients with Inflammatory Bowel Disease

Age (year)	Gender	Clinical scenario	Liver function tests	Secondary causes	Outcome	Ref.
33	F	Necropsy study (Active Ulcerative Colitis)	-	Unknown	Deceased	[32]
22	F	Necropsy study	-	Unknown	Deceased	[33]
35	M	Necropsy study (Bloody diarrhea)	Elevated AlkP	Unknown	Deceased	[34]
54	F	Necropsy study (vomiting, diarrhea)	Elevated AlkP	Unknown	Deceased	[34]
22	F	Active Ulcerative Colitis	Elevated AST, ALT	Unknown	Survived	[35]
16	M	Abdominal pain	Elevated AST, ALT, AlkP	None	Survived	[43]
40	F	Restorative proctocolectomy	Elevated AlkP	Polycythemia vera	Survived	[36]
32	M	Fever asthenia	Elevated AST, ALT	Antiphospholipid antibody	Survived	[37]
11	F	Jaundice Hepatosplenomegaly	Normal	Polycythemia vera	Survived	[44]
? (Gn)	F	Thrombotic complications, needed liver transplant	-	Antiphospholipid antibody, Protein C deficiency	Survived	[45]
27 (Kn)	F	Fever, Vomiting, Hematochezia	Elevated AST; Normal ALT	Probable Protein C deficiency	Survived	[46]
14	F	Bloody diarrhea	Normal	None	Survived	[47]
12	F	Bloody diarrhea	Normal	None	Survived	[30]
33	F	RUQ Abdominal Pain	Normal	Polycythemia vera	Survived	[28]

Cases are organized by publication date with references (Ref.) listed at far right. RUQ: Right Upper Quadrant; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; AlkP: Alkaline Phosphatase; Gn: Article written in German; Kn: Article written in Korean.

by Brinson *et al* in 1988[35]. This patient was a 22 year old female who had an active flare up of UC and elevated liver enzymes. Whiteford *et al* 1999[36] reported the second case to be diagnosed in a living patient, believed to be secondary to polycythemia that was unmasked after restorative proctocolectomy. Apparently, this patient's polycythemia went initially undetected due IBD-associated chronic blood loss from her gastrointestinal tract. In 2000, Praderio *et al* reported a third adult case in a patient who was found to have coexisting antiphospholipid antibody syndrome[37]. In 2009, a fourth adult case was reported by Vassiliadis T *et al* in a 33 year old female secondary to polycythemia[28]. This patient required a transjugular intrahepatic portosystemic shunt (TIPS) and thereafter was treated with anticoagulants for BCS and corticosteroids for IBD. Our patient will be the fifth reported adult case, but the first adult patient presenting without any evidence of classical/inherited coagulation disorder after extensive work-up. Since most of the cases were female patients it is possible that female gender is an independent risk factor; however, it is difficult to draw such conclusions based on the limited number of cases available for analysis.

We postulate that our patient developed a hepatic vein thrombus secondary to an IBD-associated hypercoagulable state exacerbated during an acute flare up of UC. The absence of evidence of a detectable thrombus in an abdominal CT scan administered 2 mo prior to admission supports the temporal relationship between thrombus development and acute flare up of her IBD. Although our patient's serum transaminase levels were not severely elevated on admission, it is possible that her abdominal pain was, at least partially, related to early venous congestion associated with the hepatic vein thrombus we discovered when evaluating for causes of intractable abdominal pain. It is noteable that our patient responded well to anticoagulation and that her UC was brought to remission, with both factors likely contributing to the resolution of her hepatic vein thrombus.

It is plausible that other unique factors associated with our patient's disease predisposed her to VTE and BCS. While our patient was found to have *Clostridium difficile* toxin positive stool on admission, the precise contribution of this finding to her development of BCS is difficult to assess. Many experts believe that *Clostridium difficile*-associated colitis can precipitate an IBD-flare up; however, whether this was causative in our patient is not clear. However, our search of the literature revealed no reported relationship between *Clostridium difficile*-associated colitis and BCS in patients with or without IBD. One could hypothesize the development of *Clostridium difficile*-associated colitis in our patient exacerbated (or even caused) her IBD flare leading to an even greater degree of local and systemic inflammation in our patient, thus putting her at greater risk for VTE and, more specifically BCS, for reasons discussed above.

The diagnosis of BCS can be made in patients who sometimes present with abdominal pain, ascites and hepatomegaly or with other findings raising a high level of suspicion in the clinician. The diagnostic modalities that have been found to be most helpful are Doppler ultrasound[38] and Computed tomography[39]. Magnetic Resonance Angiography has been shown in a few studies to be more accurate in delineating the hepatic vasculature to more precisely define the location of the obstruction[40]. Nevertheless, clear cut indications for MRI over CT have not been established. The gold standard for diagnosis is hepatic venography but it is more invasive and is typically performed when less invasive methods of evaluation are equivocal or negative. Liver biopsy can be diagnostic in some acute and subacute cases. One study by Tang TJ *et al* suggested that there was no evidence for a relationship between early liver pathology and survival[41]. However, the Child-Pugh score, serum ALT levels and evidence of porto-systemic shun-

ting appear to be prognostic indicators for patients with BCS[42]. Treatment guidelines for BCS were established in 2009 by the American Association for the Study of Liver Diseases (AASLD) (www.aasld.org). In summary, anticoagulation should be initiated immediately and continued for life unless contraindicated. An extensive workup for secondary causes of hypercoagulability should be performed. In symptomatic patients, percutaneous angiography may be helpful to look for venous obstruction and stents may be placed if necessary. TIPS is reserved for those not improving with anticoagulation and who have failed other management strategies. Liver transplantation should be considered for fulminant liver failure or failure to respond to TIPS. Medical therapy alone is recommended in patients without evidence of ongoing hepatic necrosis[42].

This case, along with the previous reports outlined above, recapitulates the need for a high level of suspicion for VTE in patients presenting with IBD.

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