Ulcerative Colitis Diagnosed in a Patient with Venous Thromboembolism

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Venous thromboembolism (VTE) is one of the serious extraintestinal manifestations of inflammatory bowel disease (IBD). Although thromboembolic episodes in the form of either deep venous thromboembolism and/or pulmonary embolism (PE) are infrequently observed in IBD patients, these patients are at increased risk for developing thromboembolic events as compared with patients who do not have IBD.[1–4] In addition, VTE is associated with a high mortality rate in IBD patients.[3,5,6] This article presents the case of a man who was hospitalized with massive PE and deep vein thromboembolism and subsequently was diagnosed with underlying ulcerative colitis.

CASE PRESENTATION

Initial Presentation and History

A 61-year-old man presented to the emergency department (ED) complaining of shortness of breath. The patient reported that onset of exertional dyspnea with decreased exercise tolerance occurred 1 month prior to presentation, which significantly limited his daily activities. The patient denied chest pain or any other respiratory signs and symptoms but noted swelling of his left lower extremity 1 week prior to admission. Three days prior to admission, he arrived from St. Martin after a 4-hour flight.

On review of systems, the patient related a 3-month history of intermittent diarrhea with bloody stools. The patient reported that he had experienced a similar episode approximately 11 years ago. At that time, colonoscopy was unrevealing, and his symptoms resolved spontaneously without treatment. He denied recent fever, cough, hemoptysis, nausea, vomiting, bloating, abdominal cramps, orthopnea, paroxysmal nocturnal dyspnea, arthralgias, or myalgias, but he stated that he had lost 30 to 40 lb within the last 6 months. He also noted urinary frequency along with weak urinary stream. The patient was employed as a mechanic. He denied using any daily medications, ethanol, cigarettes, or recreational drugs. The patient had no past history of allergies or surgery, and the family history was negative for both hypercoagulable states and malignancy.

Physical Examination

In the ED, the patient's vital signs were as follows: blood pressure, 131/70 mm Hg; heart rate, 109 bpm; respiratory rate, 20 breaths/min; temperature, 97.9°F; and oxygen saturation by pulse oximeter, 99% on room air. The patient was 5 ft 6 in and markedly obese (258 lb with a body mass index of 42 Kg/m^2). He displayed no acute respiratory distress at rest. On physical examination, there were no signs of pallor of conjunctivae or jugular venous distension. The lungs were clear on auscultation. The patient was slightly tachycardic, without any murmurs, rubs, or gallops. The abdominal examination was unremarkable, with no rectal mass found on digital examination. The prostate was enlarged but otherwise unremarkable. He had bilateral 2+ pitting pedal edema and the left calf muscle was tender on palpation.

Laboratory and Imaging Studies

Laboratory studies ordered in the ED revealed a white blood cell count of 10,200 cells/μL (normal, 4500–11,000 cells/μL), hemoglobin of 8.0 g/dL (normal, 13.5–17.5 g/dL), hematocrit of 26.5% (normal, 41%–53%), platelet count of 528,000 cells/μL (normal, 130,000–400,000 cells/μL), prothrombin time of 12.3 sec (normal, 11.5–13.1 sec), international normalized ratio of 1.0, and activated partial thromboplastin

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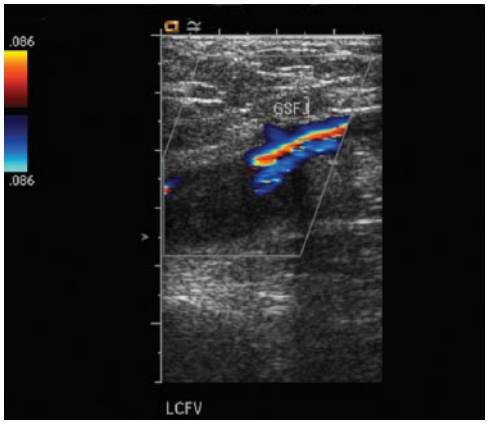

Figure 1. Color Doppler ultrasound of the case patient's left lower extremities demonstrating thrombosis in the left common femoral vein, superficial femoral vein, and a popliteal vein.

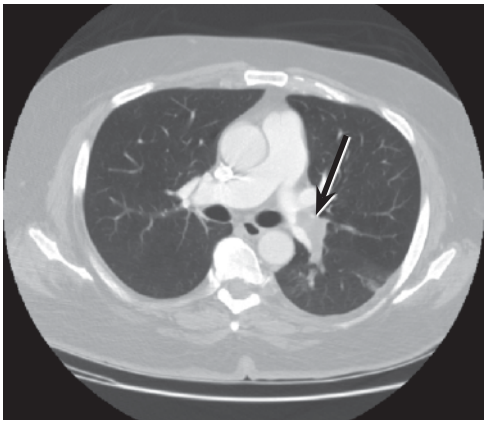

Figure 2. Chest spiral computed tomography demonstrating a 3.1-cm pulmonary embolus in the left main pulmonary artery extending into the left inferior pulmonary artery (*arrow*) with a left-sided pulmonary infarct.

time of 28.4 sec (normal, 23–33 sec). Chemistry panels were within the normal range. Stool guaiac test was positive. Serum prostate-specific antigen was 6.58 ng/mL (normal, < 4.0 ng/mL).

Color Doppler ultrasound of the lower extremities revealed thrombosis of the left common femoral vein, superficial femoral vein, and a popliteal vein (**Figure 1**). Computed tomography scan of the chest revealed extensive PE involving the left main pulmonary artery and extending into the left inferior pulmonary artery with left pulmonary infarct (**Figure 2**).

Hospital Course

The patient was admitted to the intensive care unit, and thrombophilia evaluation was performed. He was transfused with 2 units of packed red blood cells for symptomatic anemia and was started on enoxaparin 120 mg subcutaneously every 12 hours. On hospital day 4, the results of the thrombophilia evaluation became available (**Table 1**) but did not reveal any significant underlying thrombophilia. After the patient's anemia improved, a gastrointestinal work-up was undertaken on hospital day 8 to investigate for the presence of malignancy. Colonoscopy demonstrated friable edematous and erythematous mucosa, with loss of haustral markings and shallow scattered ulcerations throughout the large bowel from rectum to cecum (**Figure 3**). A small pedunculated polyp was noted in the descending colon. Biopsies revealed moderate to severely active chronic pancolitis consistent with ulcerative colitis, without evidence of dysplasia. The polyp was inflammatory and not adenomatous. Computed tomography of the abdomen and pelvis was unremarkable, except for prostate enlargement; subsequent biopsies were negative for malignancy. IBD panels were ordered (**Table 2**), which revealed elevated perinuclear antineutrophilic cytoplasmic antibody titers, which further supported the diagnosis of ulcerative colitis.

The patient was started on mesalamine 800 mg orally 3 times daily and mesalamine 4 g retention enema at bedtime. Enoxaparin was switched to warfarin after the international normalized ratio reached therapeutic levels on hospital day 13. After an unremarkable hospital course, the patient was discharged on hospital day 18. He returned to his country, which precluded further follow-up. However, his treatment plan included continuing with oral mesalamine until symptomic improvement of his IBD and anticoagulation with warfarin for at least 6 months.

DISCUSSION

IBD is a chronic condition that has extraintestinal manifestations involving the skin, eyes, joints, biliary tract, vasculature, and other organs. VTE is a life-threatening complication of IBD with mortality rates that range from 8% to 25%.[3,5,6] Although thromboembolic events are infrequent in IBD patients, cohort studies have demonstrated that the incidence of VTE is 3 to 3.6 times greater in patients with IBD as compared with control groups comprising an age- and gender-adjusted population.[1,2] The prevalence of VTE in IBD patients, which has been investigated using different methods, ranges from 1.3% to 6.2%.[1,3] In contrast to other chronic inflammatory conditions such as rheumatoid arthritis or celiac disease, IBD has been shown to be an independent risk factor for thromboembolism.[1] Although a Swedish study failed to show increased incidence of VTE in IBD patients, it

Table 1. Thrombophilia Evaluation in Case Patient

Study	Results	Reference Range
Homocysteine (μmol/L)	11.8	< 11.4
Protein C (%)	84.04	68–150
Protein S (%)	66.56	61–142
Antithrombin III (%)	38.29	78–140
Anticardiolipin antibody IgG (GPL)	30	< 22
Anticardiolipin antibody IgM (MPL)	2	10

nonetheless reported that VTE occurred at a younger age in IBD patients (mean, 53 yr) as compared with non-IBD patients (mean, 64 yr).[4] Other studies have corroborated this finding.[2,7]

Mechanisms of VTE in Patients with IBD

Despite multiple studies, the cellular basis for the hypercoagulable state found in patients with IBD remains unclear.[8] However, the underlying mechanisms for the increased VTE incidence in patients with IBD are thought to be multifactorial. Potential mechanisms that have been studied include activation of platelets, hyperhomocysteinemia and other thrombophilic disorders, and activation of the coagulation cascade.

Platelet activation due to endothelial lesions in the bowels may cause a sustained coagulation cascade, leading to generation of microthrombi in the bowel capillaries.[9] The CD40 ligand, which is derived primarily from activated platelets and exhibits prothrombotic properties, is significantly increased in IBD patients.[7] The platelets found in IBD patients overexpress the CD40 ligand protein up to 4 times and release soluble CD40 ligand, increasing its level in plasma up to 15-fold.[10]

Hyperhomocysteinemia is frequently observed in IBD patients due to reduced dietary intake and malabsorption associated with IBD. High homocysteine concentrations activate factor V in endothelial cells, which inhibits the activation of protein C and leads to an increased risk of thrombosis.[11] As such, it is hypothesized that hyperhomocysteinemia may have a role in the development of VTE in the setting of IBD.[12] Although 1 study observed an increased prevalence of hyperhomocysteinemia in IBD patients, homocysteine levels did not differ between IBD patients with venous or arterial thrombosis and those without thrombosis.[13]

Studies that examined the role of other thrombophilic disorders did not reach any clear conclusions pertaining to their mechanism in IBD patients who developed VTE. Factor V Leiden (FVL) mutation, the leading cause of inherited thrombophilia, results in activated protein C resistance that in turn causes a hypercoagulable state. The literature has shown no difference in the prevalence of the FVL mutation between IBD patients and healthy controls.[12] In addition, the prevalence of the FVL mutation in IBD patients with VTE did not differ from that found in non-IBD patients with VTE.[10,14] However, activated protein C resistance was more common in IBD patients with a history of thromboembolism as compared with healthy controls and IBD patients without a history of thromboembolism (31.3% versus 5.9% and 7%, respectively; $P < 0.01$).[7] Likewise, prothrombin gene 20210 mutation has been found in patients with IBD but is no more prevalent in patients with IBD than those without IBD.[6,7,10] Levels of antithrombin (AT) III, an endogenous thrombin inhibitor, appear to be lower in the plasma of IBD patients.[7] However, decreased AT III levels in the presence of inflammation may indicate higher use of AT III due to the more intense coagulation activity.[4,9] In addition, decreased levels of protein C and S have also been described in IBD patients, but reports are conflicting.[10,12]

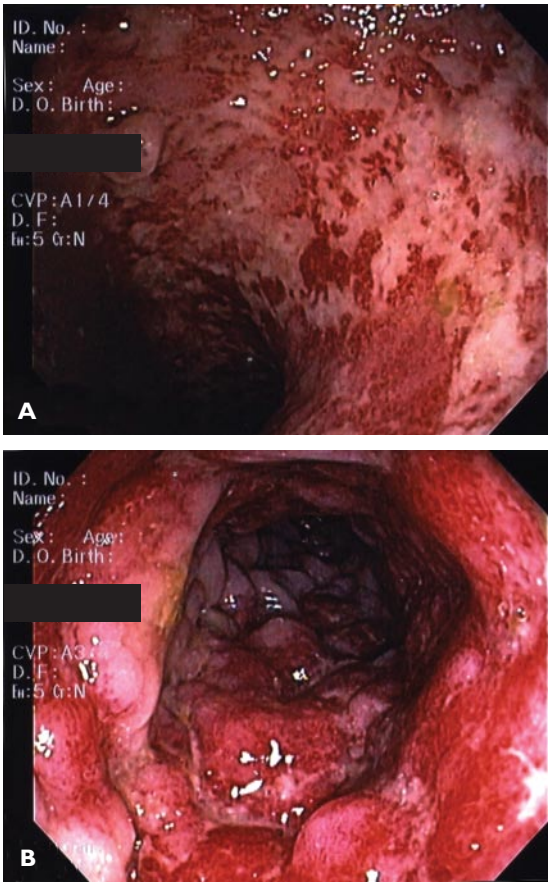

Figure 3. Colonoscopy demonstrating friable edematous and erythematous mucosa (**A**), with loss of haustral markings and diffuse proctocolitis with ulcerations (**B**).

López et al[15] have postulated that tissue factor (TF)-bearing microvesicles are central in the pathogenesis of VTE in IBD patients. By fusing with the platelets, the microvesicles transfer TF, a type I transmembrane protein, to the platelet membrane, thus increasing TF-VIIa activity, thrombin generation, and fibrin deposition at the thrombosis site.[15] Studies also have shown that endotoxin interacting with interleukin-1 and tumor necrosis factor-α can activate the coagulation cascade, and adding endotoxin to blood samples of IBD patients in vitro induces microclot formation.[1,16]

There are many established risk factors for VTE. When present, risk factors such as immobility, hospitalization, or surgery are thought to contribute to the development of thromboembolic events in IBD patients.[6] In addition, the activity and extent of IBD are significantly relevant to the increased risk of VTE.[6] In a study that defined IBD as active if the patient had any pertinent gastrointestinal symptoms within the 3-month period prior to thrombotic episodes or endoscopic or radiographic evidence of active disease, approximately 80% of IBD patients had active disease at the time of the thromboembolic episodes, and 76% of patients with ulcerative colitis had pancolonic involvement.[6] Papa et al[14] also reported that 66% of IBD patients who developed a thromboembolic event had active IBD.

As this case patient demonstrates, VTE is often a multifactorial process. Several coexisting risk factors for VTE were observed on clinical evaluation of the patient, specifically marked obesity and immobility with recent travel. Of note, work-up for an underlying etiology of VTE revealed ulcerative colitis with pancolonic involvement on colonoscopy. Ulcerative colitis was active in this patient (as evidenced by bloody diarrhea and diffuse colitis), which further increased the patient's risk for developing VTE.

Work-up for Underlying Causes of VTE

In patients who are diagnosed with VTE, further work-up is often directed at elucidating the underlying cause. Because malignancy is known to be a strong risk factor for VTE, a work-up for malignancy such as rectal examination, fecal occult blood testing (FOBT), and colonoscopy may be undertaken. In the case patient, significant weight loss, anemia, a positive FOBT, and elevated prostate-specific antigen levels suggested the presence of a possible underlying neoplasm. Although some features of the presentation suggested the presence of underlying IBD (namely diarrhea and a positive FOBT), they were nonspecific and did not automatically prompt investigations for IBD.

Comprehensive work-up for thrombophilia (ie, genetic screening for FVL or prothrombin G20210A mutations, hyperhomocysteinemia, protein C and S deficiencies, AT III deficiency, and hyperphospholipid syndrome) in IBD patients is still controversial and no clear guidelines exist.[10] However, some recommend screening for underlying thrombophilia in IBD patients with VTE to further define the prothrombotic risk, as the presence of thrombophilia will change therapeutic and prophylactic management.[6,14,17] Concurrent active IBD and a positive screening test for thrombophilia in a patient who has experienced a thrombotic event should strongly suggest implementing lifelong anticoagulation therapy.[6,10] In the case patient, the thrombophilia evaluation revealed a decreased AT III level. However, as noted earlier, active inflammation may have been responsible for this patient's lower levels of AT III,[4,9] and thus it is difficult to determine whether decreased AT III levels contributed to his VTE. Homocysteine and anticardiolipin antibody IgG levels were marginally elevated in the case patient, both indicating nonspecific findings that were not significantly abnormal.

Table 2. Specific Antibody Studies in Case Patient

Study	Results	Reference Range
P-ANCA myeloperoxidase antibody (U/mL)	10	< 6
Proteinase-3 antibody (U/mL)	< 6	< 6
ASCA IgG (U/mL)	7.0	< 20
ASCA IgA (U/mL)	14.0	< 20

ASCA = antisaccharomyces cerevisiae antibodies; P-ANCA = perinuclear antineutrophilic cytoplasmic antibody.

Management Issues

The management of an acute thrombotic event in patients with IBD and in patients without IBD is similar.[18] Currently, there are no available data that indicate whether low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is superior in the setting of acute thrombosis. In the case patient, anticoagulation with enoxaparin was promptly started once the diagnosis of VTE was established and was followed by transfusion with packed red blood cells as needed. Therapy was instituted with a LMWH despite the presence of bloody diarrhea because the benefit of treatment outweighed its risks.

Because the prothrombotic state in IBD is well established and intestinal microvascular thrombosis seems to play role in the pathogenesis of IBD, heparin has been studied as an adjuvant treatment for IBD. Apart from its anticoagulant activity, heparin is beneficial for IBD

because it has an anti-inflammatory effect that reverses endothelial dysfunction, interferes with leukocyte attachment by reducing endothelial intercellular adhesion molecule-1, prevents neutrophil diapedesis by inhibiting the neutrophil's elastase, and modulates cytokine production and thus inhibits tumor necrosis factor-α, which correlates with disease activity in both ulcerative colitis and Crohn's disease.[14,17] Several studies reported that UFH may be beneficial for treating IBD patients, especially in the setting of steroid-refractory ulcerative colitis.[17] However, data were limited in patients with Crohn's disease, and UFH cannot be recommended as a treatment modality for these patients at this time.[17] Worsening of rectal bleeding was infrequently seen following UFH treatment in these studies.[14,17] In contrast, 2 studies that examined the role of a LMWH for ulcerative colitis showed no significant clinical advantage as compared with placebo and standard treatment of ulcerative colitis.[19,20]

Because VTE recurrence is common, the utility of maintenance anticoagulation therapy in patients with IBD is debated.[12] Although prophylactic anticoagulation with heparin is not recommended for all IBD patients, it should be implemented when the benefit for prophylaxis outweighs the relative contraindication with rectal bleeding.[21] As discussed earlier, lifelong anticoagulation with warfarin should be considered when concurrent thrombophilia exists.[6] Temporary prophylactic anticoagulation with either LMWH or UFH should be strongly considered in high-risk situations (eg, immobilization or during the perioperative period), unless a contraindication for active bleeding coexists.[6,12]

SUMMARY

IBD is a well-established risk factor for VTE that confers an approximately threefold greater risk for developing VTE as compared with patients without IBD.[1,2] When investigating underlying etiologies of VTE, IBD should be included in the differential diagnosis when clinical features of IBD are present. Physicians should be aware that treatment of patients with concurrent VTE and IBD might be altered when other risk factors for thrombophilia are present. **HP**

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