

# *World Journal of Colorectal Surgery*

---

*Volume 1, Issue 1*

2008

*Article 2*

---

## Severe Deep Vein Thrombosis Complicating Surgery for Ulcerative Colitis

James V. Pasquariello\*

Jeremy P. Walco<sup>†</sup>

Michael Ombrellino<sup>‡</sup>

Rolando H. Rolandelli\*\*

\*Morristown Memorial Hospital, [jvp9286@hotmail.com](mailto:jvp9286@hotmail.com)

<sup>†</sup>Morristown Memorial Hospital, [jpwalco@cornell.edu](mailto:jpwalco@cornell.edu)

<sup>‡</sup>Morristown Memorial Hospital, [michael.obrellino@atlanticealth.org](mailto:michael.obrellino@atlanticealth.org)

\*\*Morristown Memorial Hospital, [rolando.rolandelli@atlanticealth.org](mailto:rolando.rolandelli@atlanticealth.org)

# Severe Deep Vein Thrombosis Complicating Surgery for Ulcerative Colitis

James V. Pasquariello, Jeremy P. Walco, Michael Ombrellino, and Rolando H. Rolandelli

## Abstract

**PURPOSE:** We report the case of an unusual presentation of deep vein thrombosis in a patient with ulcerative colitis. **METHODS:** We review the patient's medical records, clinical and laboratory findings, and operative reports, as well as review the applicable literature. **RESULTS:** We describe the case of a 47-year-old man who presented with a severe deep vein thrombosis during the course of ulcerative colitis. Most deep vein thromboses can be successfully treated with typical anticoagulation therapy. However, our patient was not as responsive, and his course was complicated further by surgery. **CONCLUSIONS:** Deep vein thrombosis can be caused by ulcerative colitis. By removing the inflamed colon the source of the thrombosis can be eliminated.

**KEYWORDS:** Ulcerative Colitis, Inflammatory Bowel Disease, Deep Vein Thrombosis, Hypercoagulability, Bowel Resection, Surgery

## **Severe Deep Vein Thrombosis Complicating Surgery for Ulcerative Colitis**

James Pasquariello, MD, Jeremy P. Walco, Michael Ombrellino, MD,

Rolando H. Rolandelli, MD

From the Department of Surgery, Morristown Memorial Hospital, Morristown, New Jersey

Address correspondence and reprint requests to Rolando H. Rolandelli: Department of Surgery,

Morristown Memorial Hospital, 100 Madison Avenue, Morristown, NJ 07960

Telephone: (973) 971-4105

Telefax: (973) 707-5589

Email: [Rolando.rolandelli@atlanticealth.org](mailto:Rolando.rolandelli@atlanticealth.org)

**PURPOSE:** We report the case of an unusual presentation of deep vein thrombosis in a patient with ulcerative colitis. **METHODS:** We review the patient's medical records, clinical and laboratory findings, and operative reports, as well as review the applicable literature. **RESULTS:** We describe the case of a 47-year-old man who presented with a severe deep vein thrombosis during the course of ulcerative colitis. Most deep vein thromboses can be successfully treated with typical anticoagulation therapy. However, our patient was not as responsive, and his course was complicated further by surgery. **CONCLUSIONS:** Deep vein thrombosis can be caused by ulcerative colitis. By removing the inflamed colon the source of the thrombosis can be eliminated. [Key words: Ulcerative Colitis; Inflammatory Bowel Disease; Deep Vein Thrombosis; Hypercoagulability; Bowel Resection; Surgery]

#### CASE REPORT:

The patient is a 47 year-old male, who presented an eight year history of ulcerative colitis. Upon initial presentation the patient had complaints of lower abdominal pain, bleeding, and up to twenty bowel movements a day. He had lost weight and was in extreme discomfort. A colonoscopy revealed pancolitis. In addition to Prednisone, 40 mg per day, he received 5-aminosalicylic acid 4800 mg, daily; Loperamide, as needed; Dicyclomine 30 mg, daily; Valsartan 80 mg; and Atenolol 25 mg. He was a smoker and had stopped right before his colitis symptoms began. Seven months prior to his initial presentation he was diagnosed and treated for a deep vein thrombosis (DVT), for which he was given heparin and warfarin.

The patient was admitted prior to his proctocolectomy and received heparin. On the day of surgery a removable inferior vena cava filter (G2 Bard<sup>TM</sup>) was placed. His venogram

demonstrated no evidence of thrombus in the inferior vena cava or iliac veins. He subsequently underwent a total proctocolectomy with ileal pouch anal anastomosis, a temporary diverting ileostomy, and a mucous fistula creation. His postoperative course was complicated by left leg swelling. On postoperative day 6, venous duplex showed right external iliac vein, common femoral, peroneal, and left femoral vein thromboses. He was sent home on low molecular weight heparin, bridging to warfarin, as well as a Prednisone taper.

On postoperative day 16 he suddenly developed bleeding per anus and per ileostomy. His INR was 2.89 and after fluid resuscitation his hemoglobin was 5.4 and hematocrit 15.7. He was admitted to the hospital and required 8 units of packed red cells to restore his loss of blood, as well as 8 units of fresh frozen plasma, 1 unit of cryoprecipitate, and vitamin K to reverse his INR to normal. Once bleeding subsided he was started again on heparin and warfarin. He remained hospitalized until his INR reached therapeutic levels.

On postoperative day 29 he had worsening edema of his lower extremities which severely interfered with ambulation. A repeat venous duplex showed bilateral ilio-femoral vein thrombosis, bilateral femoral and popliteal vein thromboses, and right peroneal vein thrombosis. Chemical thrombolysis was not considered because of recent surgery and subsequent bleeding. He was fitted with compression stockings, which he wore intermittently, and therefore showed only minimal improvement of his symptoms.

Two months after his initial surgery, the patient had his ileostomy reversed. He was placed on heparin prior to the procedure, and his warfarin regiment was ceased. He did well postoperatively, and the swelling in his legs had shown remarkable improvement. Therefore, he was sent home with no anticoagulation medication.

## DISCUSSION:

The correlation between inflammatory bowel disease (IBD) and hypercoagulability, leading to thromboembolic phenomena is well documented. In clinical studies the occurrence of systemic thromboembolism in IBD patients is between 1% and 7.7% and up to 41% in postmortem studies.<sup>1</sup> These numbers may be even higher in ulcerative colitis, as compared to Crohn's disease.<sup>2</sup> Furthermore, in a population-based cohort study in 2001 by Bernstein et al. it was concluded that IBD patients have a threefold increased risk of suffering from a deep vein thrombosis or pulmonary embolism.<sup>3</sup> Miehsler et al (2004) confirmed this finding in a similar study by noting that IBD is a significant risk factor for thromboembolism and that thromboembolism is a specific feature of IBD.<sup>4</sup> Furthermore, thromboembolic events have been found to be correlated with the extent of IBD, particularly involvement of the transverse colon in ulcerative colitis.<sup>1</sup> Our patient had pancolonic involvement of the disease and therefore fits this profile.

There are various prothrombotic risks observed in IBD patients, including inflammation, fluid depletion, immobility, surgery, steroid therapy, and the use of central venous catheters.<sup>5</sup> Our patient had extensive and severe inflammation of the colon throughout the course of his disease. He also had fluid depletion, as inferred from his history of weight loss and diarrhea. The presentation of a thrombosis may also be attributed to his extended use of oral Prednisone. In a recent investigation by Huerta and colleagues (2007), it was concluded that long term use of oral corticosteroids was associated with an increased risk of venous thromboembolism.<sup>6</sup> While the initial onset of his deep vein thrombosis occurred seven months prior to his surgery, the DVT spread to both legs and worsened significantly following his bowel resection. Our patient was operated on in the lithotomy position, which is known to decrease venous blood flow.<sup>7</sup> He also

had a predisposition to DVT, and leg elevation during surgery has the potential to aggravate this complication. Our patient's surgery was long, and an operating time over five hours indicates increased risk for complications following procedures in the lithotomy position.<sup>7</sup> Finally, while the insertion of an IVC filter is done to prevent pulmonary embolisms, it is associated with an increased risk of venous thromboembolism at the insertion site.<sup>8</sup>

Factor V Leiden (FVL) is a mutation in the Factor V gene and is the most common defect associated with hypercoagulability.<sup>9</sup> The genetic disorder results in increased generation of thrombin, leading to a prothrombotic state.<sup>10</sup> Our patient tested negative for the Factor V Leiden, which is not necessarily surprising considering the lack of association between IBD and FVL. Studies by Papa et al (2000) and Zauber et al (1998) found no increase in the percentage of IBD patients with FVL, compared to a control population.<sup>11, 12</sup> Our patient also tested negative for the G20210A mutation, a mutation in the prothrombin gene. Numerous studies have confirmed that the incidence of this mutation is not increased in IBD patients.<sup>11, 13-15</sup>

Many of the same mechanisms responsible for the inflammatory response are also involved in coagulation and clotting. Therefore, extensive chronic inflammation often leads to an abnormal alteration of these factors, which can in turn lead to a hypercoagulable state and adverse thrombotic conditions. Altered hemostasis parameters involved with coagulation, fibrinolysis, and platelet aggregation and function have been observed in inflammatory bowel disease patients and represent possible causes of a prothrombotic condition. Markers of coagulation, such as prothrombin fragment 1 + 2, the antithrombin III complex, fibrinopeptide A, and fibrinopeptide B have been shown to be increased in IBD patients.<sup>1, 16</sup> Factor XIII has been shown to exhibit decreased expression in the course IBD.<sup>17, 18</sup> Protein S and Protein C are key anticoagulant factors, and decreases in their levels are critical markers for susceptibility to

thromboembolism. Prior to surgery, our patient was found to have reduced Protein C activity, which is consistent with findings that show reduced activity levels of both Protein C and Protein S in IBD patients.<sup>19, 20</sup> Not consistent, however were findings following surgery, at which time his Protein C activity, Protein S activity, and Anti-thrombin III activity were all in the normal range, while his thrombotic condition seemed to be worsening. Studies by Baglin et al. (2003) and Christiansen et al. (2005) suggest that while the afore-mentioned markers of hypercoagulability are useful in identifying underlying causes of the onset of a DVT, they are not helpful in predicting recurrence of venous thrombembolism.<sup>21, 22</sup>

While our patient does fit some of the documented criteria of an IBD patient suffering from thrombotic events, there remain some perplexing concerns. First, platelets have been shown to behave abnormally in inflammatory bowel disease. During the active phase of the disease platelet count frequently increases,<sup>1</sup> but even during inactive stages of IBD platelet aggregation responses have been shown to be enhanced.<sup>23</sup> The excessive activity of the blood coagulation system that results from the inflammatory activity of ulcerative colitis can lead to venous thrombosis if there is excessive aggregation of different clotting factors, including platelets.<sup>24</sup> In addition, the CD40 ligand, which is derived from activated platelets, has prothrombotic tendencies in addition to its proinflammatory effects.<sup>10</sup> Danese et al. have shown that CD40 levels are slightly increased in IBD patients, as compared to healthy controls.<sup>25</sup> Our patient's post-surgery CBC surprisingly showed a low platelet count, despite his ongoing and worsening DVT. A possible explanation is that the initial onset of the DVT was caused partially by excessive platelet aggregation from the inflammatory response, and even after the platelet count was dramatically reduced, the thromboses remained intact.

Another surprising finding came from our patient's homocysteine levels.

Hyperhomocysteinemia is both a proinflammatory and prothrombotic condition.<sup>26</sup> Indeed it has been found that IBD patients are more susceptible to dramatic increases in homocysteine levels, due to their decreased vitamin intake.<sup>2, 27-29</sup> Surprisingly, despite his severe bilateral DVT our patient showed low homocysteine levels, as compared with the norm, upon testing.

Hyperhomocysteinemia has been well documented as one of the key links between IBD and thromboembolic events, and this finding certainly goes against this notion. These studies, however, are preliminary and have not found many clear, indisputable, omnipresent causes of hypercoagulability leading to thromboembolism in IBD patients. In addition, many of these studies do not separate Crohn's disease and ulcerative colitis when considering thrombotic complications, and these two diseases may indeed follow different mechanisms towards a prothrombotic condition.

To treat his deep vein thrombosis and ulcerative colitis, our patient was placed on heparin, followed by warfarin. Heparin has been shown to have some effectiveness in treating ulcerative colitis when the disease is resistant to steroid therapy, as it seemed to be in our patient. Because of its anticoagulant effect, heparin has been used to prevent DVT, pulmonary embolism and unstable angina. It seems to treat inflammatory bowel disease by inhibiting the activated coagulation factor X and thrombin, both of which are involved in the formation of a deep venous thrombosis.<sup>30</sup> Following surgery, when his DVT worsened, our patient was placed on warfarin. While warfarin is not intended to treat the underlying causes of IBD,<sup>31</sup> its purpose is to treat thromboses that may arise from IBD. The warfarin did show some effectiveness in our patient prior to the reversal of his ileostomy. However, the regimen was ceased prior to this procedure,

and following the operation the DVT had almost completely resolved without the aid of anticoagulation medication.

#### CONCLUSION:

While the risk of thromboembolic complications from inflammatory bowel disease is well documented, our patient presents a unique case due to his abnormal metabolic profile. The deep vein thrombosis he developed during the course of ulcerative colitis seemed only to resolve well after his colon was removed. Therefore, it is our opinion that the DVT was caused almost exclusively by the disease. The prothrombotic condition may have been exacerbated by his position during the operation and his use of corticosteroids, but once his colon was removed and his ileostomy was reversed, the presence of the DVT was dramatically reduced. However, it remains to be seen whether or not he is completely cured from these thrombotic complications.

#### REFERENCES:

1. Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M: Inflammation and coagulation in inflammatory bowel disease: The clot thickens. *Am J Gastroenterol* 102:174-186, 2007
2. Oldenburg B, Fijnheer R, van der Griend R, van Berge-Henegouwen GP, Koningsberger JC: Homocysteine in inflammatory bowel disease: A risk factor for thromboembolic complications? *Am J Gastroenterol* 95:2825–2830, 2000
3. Bernstein CN, Blanchard JF, Houston DS, Wajda A: The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: A population-based cohort study. *Thromb Haemost* 85:430-434, 2001

4. Miehsler W, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, Grisar J, Machold K, Scholz S, Vogelsang H, Novacek G: Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 53:542-548, 2004
5. Koutroubakis IE. Therapy insight: Vascular complications in patients with inflammatory bowel disease: *Nat Clin Pract Gastroenterol Hepatol* 2:266-272, 2005
6. Huerta C, Johansen S, Wallander MA, Garcia Rodriguez LA: Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med.* 2007;167:935-943, 2007
7. Kubiak R, Wilcox DT, Dpitz L, Kiely EM: Neurovascular morbidity from the lithotomy position. *J Pediatr Surg* 33:1808-1810, 1998
8. Rondina MT, Pendleton RC, Wheelr M, Rogers GM: The treatment of venous thromboembolism in special populations. *Thromb Res.* 2007: 119:391-402, 2007
9. Jackson LM, O’Gorman PJ, O’Connell J, Cronin CC, Cotter KP, Shanahan F: Thrombosis in inflammatory bowel disease: Clinical setting, procoagulant profile and Factor V Leiden. *Qjm* 90:183-188, 1997
10. SriRajaskanthan R, Winter M, Muller A: Venous thrombosis in inflammatory bowel disease. *Eur J Gastroetnerol Hepatol* 17:697-700, 2005
11. Papa A, De Stefano V, Gasbarrini A, Chiusolo P, Cianci R, Casorelli I, Paciaroni K, Cammarota G, Leone G, Gasbarrini G: Prevalence of factor V Leiden and the G20210A prothrombin-gene mutation in inflammatory bowel disease. *Blood Coagul Fibrinolysis* 11:499-503, 2000

12. Zauber NP, Sabbath-Solitare M, Rajoria G, Mogan G: Factor V Leiden mutation is not increased in patients with inflammatory bowel disease. *J Clin Gastroenterol* 27:215-216, 1998
13. Vecchi M, Sacchi E, Saibeni S, Meucci G, Tagliabue L, Duca F, De Franchis R: Inflammatory bowel diseases are not associated with major hereditary conditions predisposing to thrombosis. *Dig Dis Sci* 45:1465-1469, 2000
14. Papa A, Dansese S, Grillo A, Gasbarrini G, Gasbarrini A: Review article: Inherited thrombophilia in inflammatory bowel disease. *Am J Gastroenterol* 98:1247-1251, 2003
15. Mahmood A, Needham J, Prosser J, Mainwaring J, Trebble T, Mahy G, Ramage J: Prevalence of hyperhomocysteinaemia, activated protein C resistance and prothrombin gene mutation in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 17:739-744, 2005
16. Chamouard P, Grunebaum L, Wiesel ML, Frey PL, Wittersheim C, Sapin R, Baumann R, Cazenave JP: Prothrombin fragment 1 + 2 and thrombin-antithrombin III complex as markers of activation of blood coagulation in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 7:1183-1188, 1995.
17. Lorenz R, Olbert P, Born P: Factor XIII in chronic inflammatory bowel diseases. *Semin Thromb Hemost* 22:451-455, 1996
18. Van Bodegraven AA, Tuynman HA, Schoorl M, Kruishoop AM, Bartels PC: Fibrinolytic split products, fibrinolysis, and factor XIII activity in inflammatory bowel disease. *Scand J Gastroenterol* 30:580-585, 1995
19. Heneghan MA, Cleary B, Murray M, O'Gorman TA, McCarthy CF: Activated protein C resistance, thrombophilia, and inflammatory bowel disease. *Dig Dis Sci* 43:1356-1361, 1998

20. Saibeni S, Vecchi M, Valsecchi C, Faioni EM, Razzari C, de Franchis R: Reduced free protein S levels in patients with inflammatory bowel disease: Prevalence, clinical relevance, and role of anti-protein S antibodies. *Dig Dis Sci* 46:637-643, 2001
21. Baglin T, Luddington R, Brown K, Baglin C: Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: Prospective cohort study. *Lancet* 362:523-526, 2003
22. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR: Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA* 293:2352-2361, 2005
23. Andoh A, Tsujikawa T, Hata K, Araki Y, Kitoh K, Sasaki M, Yoshida T, Fujiyama Y: Elevated circulating platelet-derived microparticles in patients with active inflammatory bowel disease. *Am J Gastroenterol* 100:2042-2048, 2005
24. Meijden PE, Heemskerk JW, Hamulyak K, Cate H: Classification of venous thromboembolism (VTE). *J Thromb Haemost* 3:2575-2577, 2005
25. Danese S, Katz J, Saibeni S, Papa A, Gasbarrini A, Vecchi M, Fiocchi C: Activated platelets are the source of elevated levels of soluble CD40 ligand in the circulation of inflammatory bowel disease patients. *Gut* 52:1435-1441, 2003
26. Welch GN, Loscalzo J: Homocysteine and atherothrombosis. *N Engl J Med* 338:1042-1050, 1998
27. Cattaneo M, Vecchi M, Zighetti ML, Saibeni S, Martinelli I, Omodei P, Mannucci PM, de Franchis R: High prevalence of hyperhomocysteinemia in patients with inflammatory bowel disease: A pathogenic link with thromboembolic complications? *Thromb Haemost* 80:542-545, 1998

28. Romagnuolo J, Fedorak RN, Dias VC, Bamforth F, Teltscher M: Hyperhomocysteinemia and inflammatory bowel disease: Prevalence and predictors in a cross-sectional study. *Am J Gastroenterol* 96:2143-2149, 2001
29. Danese S, Sgambato A, Papa A, Scaldaferrri F, Pola R, Sans M, Lovecchio M, Gasbarinni G, Cittadini A, Gasbarinni A: Homocysteine triggers mucosal microvascular activation in inflammatory bowel disease. *Am J Gastroenterol* 100:886-895, 2005
30. Papa A, Danese S, Gasbarinni A, Gasbarinni G: Review article: Potential therapeutic applications and mechanisms of action of heparin in inflammatory bowel disease. *Aliment Pharmacol Ther* 14:1403-1409, 2000
31. Michell NP, Lalor P, Langman MJ: Heparin therapy for ulcerative colitis? Effects and mechanisms. *Eur J Gastroenterol Hepatol* 13:449-456, 2001