

Case Report

**Combined portal, splenic and mesenteric venous thrombosis in inactive ulcerative colitis with heterozygous mutation in MTHFR gene:
A rare case of thrombophilia**

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Abstract

Thrombophilia is a rare but potentially catastrophic phenomenon occurring in patients having tendency of thrombosis. It may lead to serious complications. The etiology of thrombophilia is thought to be multifactorial and related to both acquired and inherited factors. Inflammatory bowel disease is an acquired cause of thrombophilia. Thromboembolic events are seen during inflammatory bowel disease, especially during the active period of the disease. In inflammatory bowel disease, thrombus formation in portal, splenic and mesenteric veins are not common. Besides, the association of genetic disorders related to metabolism of homocysteine with inflammatory bowel disease has been evidenced, especially in Crohn disease and rarely in ulcerative colitis. We present a rare case of ulcerative colitis in association with combined portal, splenic and mesenteric vein thrombosis. The patient was recently diagnosed with the disease which was in the inactive period. Interestingly, our patient was also heterozygous for the mutation in methylenetetrahydrofolate reductase (MTHFR) gene.

KEYWORDS: Thrombophilia, Inflammatory Bowel Disease, Ulcerative Colitis, Portal Vein Thrombosis, Mesentery Vein Thrombosis, Splenic Vein Thrombosis, Methylenetetrahydrofolate Reductase Gene.

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Thrombophilia is not a common phenomenon. It occurs in patients having a tendency of thrombosis and may cause serious complications¹. Thrombophilia has congenital and acquired causes. A rare acquired cause has been determined as inflammatory bowel disease (IBD). Thromboembolic complications of IBD and ulcerative colitis (UC) were first described in 1936.² Since this initial observation, multiple reports have suggested an association between both arterial and venous thromboembolism in the setting of UC.³⁻⁹ In community based studies, the incidence of thromboembolism in the general population was as high as 1 in 1000,¹⁰ depending on age and other risk factors. Published venous thromboembolism rates among series of patients with UC range from 1.3% to

6.2%,^{11,12} whereas in the postmortem period, the incidence has been reported as high as 41%.¹³

Deep vein thrombosis of the lower limbs and pulmonary embolism are the most common thromboembolic phenomena seen in patients with UC.^{8,14} However, uncommon cases have been reported of thrombosis in other veins and arteries such as cerebral, retinal vessels,¹⁵ peripheral arteries,¹⁶ mesenteric,⁵ splenic¹⁷ and portal veins⁸ and transverse sinus.¹⁸

Thrombotic complications were suggested to be increased during the active periods of UC.¹⁹ Standard thrombophilia evaluation studies found several factors such as hospitalization, immobilization, malignancy and recent surgery to contribute to increased thromboembolic complications in patients with UC.

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Recent data suggests thromboembolism as a disease-specific extraintestinal manifestation of UC which is developed as the result of multiple interactions between acquired and genetic risk factors. There is evidence indicating an imbalance of procoagulant, anticoagulant and fibrinolytic factors predisposing patients with IBD to thrombosis.²⁰ The genetic factors that have been suggested to interfere in the thrombotic manifestations of IBD include factor V Leiden, factor II (prothrombin, G20210A), methylenetetrahydrofolate reductase (MTHFR) gene mutation, plasminogen activator inhibitor type 1 (PAI-1) gene mutation and factor XIII (val34leu).²¹⁻²³ Mutations in MTHFR gene and related hyperhomocysteinemia have been found to be associated with thrombotic complications in UC.^{24,25}

We hereby report a rare case of thrombophilia presented with only abdominal pain. It was accidentally diagnosed as UC having portal, splenic, and mesenteric vein thrombosis. There is also an associated heterozygosity for the mutation in MTHFR gene.

Case Report

A 42 year old male patient with a complaint of intermittent abdominal pain lasting for 5-7 days presented to the Internal Medicine Out-patient Clinic of Ankara Education and Research Hospital in August 2010. He did not have any other complaint or history of any disease. He was not smoking. On physical examination, he was alert and oriented with a temperature of 36.8°C, a pulse of 82 bpm and a blood pressure of 120/60 mmHg. Cardiac exam was normal with regular heart rate and rhythm, normal heart sounds and no murmurs. Physical examination was unremarkable other than mild generalized tenderness. Laboratory data included a hemoglobin of 13.3 g/dl (normal range: 11.7-15.5), white blood count of 10,500 cells/mm³ (normal range: 4.5-11) and platelets of 131,000 cells/mm³ (normal range: 150-450). Biochemical tests were all within normal limits except a slight elevation in aminotransferases (aspartate aminotransferase: 54 U/L (normal range: 0-35), alanine

aminotransferase: 57 U/L (normal range: 0-35)). Chest X ray film did not show any acute process and electrocardiogram showed normal sinus rhythm and no ST and T wave changes. Abdominal ultrasonography (USG) revealed portal vein thrombosis. In order to ascertain the hematological status of the patient, a blood sample was withdrawn to determine thrombophilic parameters.

After the patient was accepted in our clinic, treatment was commenced with low molecular weight heparin (enoxaparin, 0.4 cc, once a day). On the eighth day of his admission, abdominal pain worsened and abdominal defence was detected. A new USG was done and all branches of the portal vein, inferior mesenteric vein and proximal part of splenic vein were found to be thrombotic. Moreover, necrosis was seen in some parts the small bowel. The patient was transferred to the surgery department for an emergent operation. During the operation, small bowel resection, 250 cm from the ligament of Treitz, was performed. Cholecystectomy was also conducted as gallbladder was distended and necrosed. After the operation, the patient did not experience short bowel syndrome, his status stayed stable and his abdominal pain subsided.

There was no abnormality in the plasma sent to the laboratory before the operation. The thrombophilic parameters on admission are presented in Table 1. Extensive laboratory workup for thrombophilia including measurements of factor V Leiden, factor VR2, prothrombin G20210A and lupus anticoagulants showed no abnormality. However, the patient was found to be heterozygous for the MTFHR gene both in C677T and A1298C alleles.

In order to exclude any malignancy or IBD, colonoscopy was performed and caecum was reached. In the regions of rectum, rectosigmoid junction, descending colon, splenic flexure, and approximately through the middle of transverse colon, hyperemic fragile, oedematous mucosa and decreased vascular pattern were observed. There were several pseudopolyps, especially in descending colon section.

Table 1. Thrombophilic parameters of the patient on admission

Parameter	Findings
C- reactive protein (mg/dl)	15.1
Platelets (cells/mm ³)	131.000
ESR (mm/h)	58
APTT(s)	27.5
PT (s)	12.5
INR (%)	1.1
Fibrinogen (g/L)	4.8
Homocysteine (mmol/L)	12.3
Folic acid /ng/ml)	9.0
Vitamin B ₁₂ (pg/ml)	534.0
D-Dimer (μg/ml)	1195.0
Antithrombin III (%)	111.0
Factor VII (%)	27.8
Factor VIII (%)	134.0
Protein S (%)	84.0
Protein C (%)	111.0

ESR: Erythrocyte sedimentation rate; APTT: Activated partial thromboplastin time; PT: Prothrombin time; INR: International normalized ratio.

The mucosa after the middle of transverse colon was normal. These findings revealed UC. While the patient had chronic portal vein thrombosis and had been operated because of acute splenic and mesenteric venous thrombosis, subcutaneous enoxaparin (0.6 cc, twice a day) and oral warfarin treatment (2.5 mg, once

a day) were started. After three days, according to suitable international normalized ratio (INR) levels, enoxaparin was stopped and warfarin dose was adjusted to 5 mg. Meselamine (500 mg, three times a day) was also prescribed. He was discharged home in a stable condition on meselamine and warfarin.

Table 2. Causes of thrombophilia

Congenital causes	Acquired causes
- Mutation of Factor V Leiden	- Malignity
- Mutation of Prothrombin G20210A	- Surgery, especially orthopedic
- Deficiency of Protein S	- Presence of central venous catheterism
- Deficiency of Protein C	- Trauma
- Deficiency of Antithrombin	- Pregnancy
- Hyperhomocysteinemia (due to deficiency of cystathionine beta synthase, methylenetetrahydrofolate reductase and methionine synthase)	- Oral contraceptive agents
- Deficiency of heparin cofactor II	- Hormone replacement therapy
- Deficiency of plasminogen	- Activated protein C resistance without gene mutations
- Deficiency of Factor XI	- Increase in factor VIII
- Dysfibrinogenemia	- Tamoxifen
- Increase in factor VIII	- Immobilization
- Increased activity of factor VIII coagulant	- Long travel
- Congenital venous abnormalities	- Congestive heart failure
	- Hyperhomocysteinemia due to deficiencies of vitamins or non-genetic causes
	- Antiphospholipid antibodies
	- Myeloproliferative diseases
	- Paroxysmal nocturnal hemoglobinuria
	- Inflammatory bowel disease
	- Nephrotic syndrome
	- Hyperviscosity
	- Hyperleukocytosis
	- Sickle cell anemia

Discussion

Thrombophilia does not have a unique description accepted by all authors. However, the term has been defined as either congenital or acquired thrombotic tendencies. Nowadays, it is defined more usefully covering conditions not directly related to homeostatic system, such as hyperhomocysteinemia. Thrombophilia has congenital and acquired causes (Table 2).¹ Although IBD is a rare cause of thrombophilia, it has been accepted as an independent risk factor for thromboembolism.¹¹ The frequency of thromboembolic events has varied between 1.3%¹² to 6.2%¹¹ among patients with UC. In a review of 7199 patients with IBD (half of whom had UC) over the course of 11 years, 1.3% had a thromboembolic event.¹² The mortality of those who had thromboembolism was 25% during the acute thrombotic event. This emphasizes the importance of understanding the risk for thromboembolism in this group of patients and the need to identify those who would benefit from pharmacological prophylaxis.

It was stated that thrombotic complications increased in active periods of UC.¹⁹ Our patient had neither symptoms nor diagnosis of UC before the thromboembolic events. Like patients of Irving,²⁶ he was not in the active period of the disease. Increased platelet aggregation was accepted to be responsible, at least in part, for thromboembolism that occurs in the setting of active inflammation.²⁶ Webberley et al. found that spontaneous platelet aggregation occurred *in vitro* in platelets isolated from 30% of patients with active IBD but not in platelets from control subjects.²⁷ Increased platelet aggregation in IBD may be related to an enhanced CD40/CD40L system which is a key regulator and amplifier of immune reactivity and is activated in IBD. Some investigators had shown that both UC and Crohn disease (CD) patients with clinically active disease have significantly greater expression of this immunoregulatory and pro-inflammatory molecule when compared with healthy controls.²⁸ However, it cannot be predicted whether or not increased platelet aggregation occurs in patients that are in clinical remission with no evidence

of systemic inflammation. Interestingly, two authors observed that 56%⁶ and 77%¹² of their patients with IBD developed peripheral venous thromboses during a period of clinical remission. These authors suggested that clinically detectable systemic inflammation had little role in the pathogenesis of thrombosis, although undetected inflammation could not be excluded. The discrepancy between their results and ours may be explained by the difference in the site of thrombotic event. In our patient, thrombosis occurred in portal, splenic and mesenteric veins, while their patients had thrombotic peripheral veins which are accepted as common places of thrombosis.

It was also observed that the extent and distribution of colonic disease correlated with thromboembolic risk.²⁹ Jackson et al. found all the subjects with CD to have ileocolonic disease and those with UC to have pancolonic disease.⁶ Unlike these observations, our patient did not have pancolitis. Moreover, in our patient, the perioperative period was not a risk factor for development of thromboembolism in contrast to studies of Hatoum⁵ and Fischera.³⁰

There is evidence indicating that genetic factors such as factor V Leiden, factor II (prothrombin, G20210A), MTHFR, plasminogen activator inhibitor type 1 (PAI-1) gene mutation and factor XIII (val34leu) contribute to the thrombotic manifestations of IBD.^{21-23,31,32} MTHFR is involved in the one-carbon cycle, which is of importance for nucleotide synthesis and methylation of DNA, membranes, proteins and lipids. Most common MTHFR polymorphisms are C677T and A1298C. Mutations in this gene result in a decrease of the enzyme activity that leads to mild hyperhomocysteinemia.³³ A study suggested mutations in this gene for allele C677T and A1298C to be a tendency to associate with coronary artery disease, in both homozygous and heterozygous carriers even when blood homocysteine levels were not elevated.³⁴ Our patient, whose homocysteine level was not elevated, was heterozygous for both C677T and A1298C alleles of MTHFR gene.

Usually in UC, venous thromboembolism

manifests as lower extremity deep venous thrombosis and pulmonary embolism.^{8,14} Rare cases of UC patients have been described with thrombus formation at uncommon sites such as the portal or mesenteric vein.^{5,8,11,12} Splenic thromboembolism has been even rarer.¹⁷ The majority of reported cases of mesenteric thrombosis in association with UC have been arterial, although venous thromboembolism has also been described.^{14,27} Mesenteric, splenic and portal vein thrombosis were predominantly encountered as postsurgical complications.^{5,6,12,17,35} In our patient with UC, three rare thromboembolic phenomena, including portal vein, inferior mesenteric vein and splenic vein, were observed without a history of surgery.

Our patient presented nonspecific symptoms that would not immediately raise clinical suspicion of thromboembolism. The overall mortality of such complications in patients with UC has been estimated to be very high. We think that appropriate management begins with rapid diagnosis. We therefore recommend that patients with IBD should be managed with high index of suspicion of thromboembolism.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

GG and AC designed the study. AG and NE collected the data. GG, YA, and BE analyzed and interpreted the data. All authors have read and approved the final manuscript.

References

1. Bauer KA, Lip GY. Evaluation of the patient with established venous thrombosis. [Online]. [cited 2007 January 15]. Available from: URL: <http://www.uptodate.com>
2. Bagen J, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. *Arch Intern Med* 1936; 58(1): 17-31.
3. Saleh T. Left Ventricular Thrombosis in Ulcerative Colitis. *Case Rep Gastroenterol* 2010; 4(2): 220-3.
4. Tabibian JH, Lada SJ, Tabibian N. Combined inferior vena cava & renal vein thromboses: case and synopsis of thromboembolism in inflammatory bowel disease. *Medscape J Med* 2008; 10(1): 6.
5. Hatoum OA, Spinelli KS, Abu-Hajir M, Attila T, Franco J, Otterson MF, et al. Mesenteric venous thrombosis in inflammatory bowel disease. *J Clin Gastroenterol* 2005; 39(1): 27-31.
6. Jackson CS, Fryer J, Danese S, Vanagunas A, Polensky S, Buchman AL. Mesenteric vascular thromboembolism in inflammatory bowel disease: a single center experience. *J Gastrointest Surg* 2011; 15(1): 97-100.
7. Wang JY, Terdiman JP, Vittinghoff E, Minichiello T, Varma MG. Hospitalized ulcerative colitis patients have an elevated risk of thromboembolic events. *World J Gastroenterol* 2009; 15(8): 927-35.

In conclusion, our patient had a rare cause of thrombophilia, i.e. UC. He was exceptional for the sites of thrombosis, and for combined portal, mesenteric and splenic venous thrombosis, which were seen together. He was not a usual case, as thromboembolic complication of UC was seen in an inactive period without any history of operation. In addition, his disease was not extensive. Since uniqueness of the presented symptoms contribute to the late diagnosis in these patients, an increased awareness of the association between IBD and thromboembolism in usual sites may help to diagnose a thrombophilic case in an early stage, when treatment options show a better outcome. It is important to recognize that even in the absence of clinically significant inflammation, devastating thrombosis may occur. Furthermore, our patient was also heterozygous for two alleles of MTHR gene without hyperhomocysteinemia. We also recommend screening a patient with thrombophilia for predisposing genetic factors, especially in young age. Furthermore, even an acquired cause such as IBD can be diagnosed.

8. Palkovits J, Hafner M, Rand T, Vogelsang H, Kutilek M, Gangl A, et al. Portal vein thrombosis in ulcerative colitis complicated by bleeding from gastric varices. *Inflamm Bowel Dis* 2007; 13(3): 365-6.
9. Kafkas NV, Deboneras CC, Babalis DK. Massive pulmonary embolism and ulcerative colitis. *Hellenic J Cardiol* 2008; 49(5): 365-70.
10. Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Thrombolysis* 2006; 21(1): 23-9.
11. Miehsler W, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004; 53(4): 542-8.
12. Talbot RW, Heppell J, Dozois RR, Beart RW, Jr. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* 1986; 61(2): 140-5.
13. Irving PM, Pasi KJ, Rampton DS. Thrombosis and inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2005; 3(7): 617-28.
14. 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* 1997; 90(3): 183-8.
15. Schneiderman JH, Sharpe JA, Sutton DM. Cerebral and retinal vascular complications of inflammatory bowel disease. *Ann Neurol* 1979; 5(4): 331-7.
16. Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. *Am J Gastroenterol* 2009; 104(6): 1445-51.
17. Okada T, Sasaki F, Minagawa N, Naito S, Kobayashi R, Kubota M, et al. Postoperative portal and splenic vein thrombosis in children: identification of risk factors. *Pediatr Surg Int* 2005; 21(11): 918-21.
18. Oztoprak S, Ozdil S, BesIsIk F, DemIr K¹, akalolu Y, YegInsü O, et al. A Case of Ulcerative Colitis with Thrombotic Complication Diñç DIñçer. *Gastroenterohepatoloji* 2001; 12(1): 41-3.
19. Handin RI. Bleeding and thrombosis. In: Braunwald E, editor. *Harrison's principles of internal medicine*. 15th ed. New York: McGraw-Hill; 2001. p. 354-60.
20. Tsiolakidou G, Koutroubakis IE. Thrombosis and inflammatory bowel disease-the role of genetic risk factors. *World J Gastroenterol* 2008; 14(28): 4440-4.
21. Yazici A, Senturk O, Aygun C, Celebi A, Caglayan C, Hulagu S. Thrombophilic risk factors in patients with inflammatory bowel disease. *Gastroenterol Res* 2010; 3(3): 112-9.
22. Jiang Y, Zhao J, Jiang T, Ge L, Zhou F, Chen Z, et al. Genetic polymorphism of methylenetetrahydrofolate reductase G1793A, hyperhomocysteinemia, and folate deficiency correlate with ulcerative colitis in central China. *J Gastroenterol Hepatol* 2010; 25(6): 1157-61.
23. Lijfering WM, Brouwer JL, Veeger NJ, Bank I, Coppens M, Middeldorp S, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. *Blood* 2011; 113(21): 5314-22.
24. Peyrin-Biroulet L, Rodriguez-Gueant RM, Chamailard M, Desreumaux P, Xia B, Bronowicki JP, et al. Vascular and cellular stress in inflammatory bowel disease: revisiting the role of homocysteine. *Am J Gastroenterol* 2007; 102(5): 1108-15.
25. Jiang Y, Zhao J, Xu CL, Cao SG, Lin LM, Lei Y, et al. The relationship of methylenetetrahydrofolate reductase G1793A gene polymorphism, hyperhomocysteinemia and ulcerative colitis. *Zhonghua Nei Ke Za Zhi* 2010; 49(8): 675-9.
26. Irving PM, Macey MG, Feakins RM, Knowles CH, Frye JN, Liyanage SH, et al. Platelet-leucocyte aggregates form in the mesenteric vasculature in patients with ulcerative colitis. *Eur J Gastroenterol Hepatol* 2008; 20(4): 283-9.
27. Webberley MJ, Hart MT, Melikian V. Thromboembolism in inflammatory bowel disease: role of platelets. *Gut* 1993; 34(2): 247-51.
28. Danese S, Katz JA, Saibeni S, Papa A, Gasbarrini A, Vecchi M, et al. Activated platelets are the source of elevated levels of soluble CD40 ligand in the circulation of inflammatory bowel disease patients. *Gut* 2003; 52(10): 1435-41.
29. Solem CA, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol* 2004; 99(1): 97-101.
30. Fichera A, Cicchiello LA, Mendelson DS, Greenstein AJ, Heimann TM. Superior mesenteric vein thrombosis after colectomy for inflammatory bowel disease: a not uncommon cause of postoperative acute abdominal pain. *Dis Colon Rectum* 2003; 46(5): 643-8.
31. Lindhoff-Last E, Luxembourg B. Evidence-based indications for thrombophilia screening. *Vasa* 2008; 37(1): 19-30.
32. Tsiolakidou G, Koutroubakis IE. Thrombosis and inflammatory bowel disease-the role of genetic risk factors. *World J Gastroenterol* 2008; 14(28): 4440-4.
33. Dhar S, Chatterjee S, Ray S, Dutta A, Sengupta B, Chakrabarti S. Polymorphisms of methylenetetrahydrofolate reductase gene as the genetic predispositions of coronary artery diseases in eastern India. *J Cardiovasc Dis Res* 2010; 1(3): 152-7.

34. Szczeklik A, Sanak M, Jankowski M, Dropinski J, Czachor R, Musial J, et al. Mutation A1298C of methylenetetrahydrofolate reductase: risk for early coronary disease not associated with hyperhomocysteinemia. *Am J Med Genet* 2001; 101(1): 36-9.
35. Millan M, Hull TL, Hammel J, Remzi F. Portal vein thrombi after restorative proctocolectomy: serious complication without long-term sequelae. *Dis Colon Rectum* 2007; 50(10): 1540-4.

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