November 2015

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**Recommended Citation**

Patel, Pranav; Hasan, Adey; Al Shathir, Mudher; Atia, Antwan N; and Young, Mark (2015) "Ischemic Stroke at the Time of Diagnosis of Ulcerative Colitis," *Tennessee Medicine E-Journal*: Vol. 1: Iss. 4, Article 11.  
Available at: [http://ejournal.tnmed.org/home/vol1/iss4/11](http://ejournal.tnmed.org/home/vol1/iss4/11)

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Ischemic Stroke at the Time of Diagnosis of Ulcerative Colitis
By Pranav Patel, MD; Adey Hasan, MD; Mudher Al Shathir, MD; Antwan Atia, MD; and Mark Young, MD

ABSTRACT
Thromboembolism (TE), especially arterial, is underestimated in patients with acute exacerbation of ulcerative colitis (UC). We report a case of stroke at the time of diagnosis of UC with a discussion of the potential mechanisms behind this event.

A 48-year-old male with body mass index (BMI) of 25.2 kg/m, whose only preventable risk factor is smoking, had never been diagnosed with Inflammatory Bowel Disease (IBD) and had no other comorbidities like diabetes mellitus, hypertension or dyslipidemia, presented with abdominal pain and bloody diarrhea. He was diagnosed with UC and developed an ischemic stroke nine days after cessation of daily aspirin, which he was taking prior to admission.

We hope this report will increase the awareness and understanding of this complication.

BACKGROUND
TE is a well-recognized complication of IBD for more than 60 years, with an incidence that varies between one and eight percent. It was reported in 39 percent of patients who died with a diagnosis of UC in post-mortem study. The mortality among patients with thromboembolic complications of UC is very high and reached 25 percent. These TE complications include pulmonary embolism, cerebral venous sinus thrombosis, stroke, mesenteric ischemia, myocardial infarction and peripheral limbs ischemia. In general, venous thromboembolism is more common than arterial. In literature, correlation between the incidence of TE, degree of bowel involvement and the intensity of UC attacks has been suggested.

CASE REPORT
A 48-year-old male with a history of smoking, well-controlled hyperlipidemia with low-density lipoprotein of 74 mg/dL and total cholesterol of 161 mg/dL, presented with abdominal pain that was worse on defecation and bloody diarrhea of nine days duration. The patient was on 81mg of aspirin daily. On presentation, his blood pressure was 110/62 mm Hg, pulse rate was 104 beats/minute, temperature 98.2 F and respiratory rate of 18/minute. The initial hemoglobin was 15.9 g/dL, white blood cell count 12.9 x 10/mm and platelets 323 x 10/mm. Computerized tomography (CT) of the abdomen showed diffuse thickening of the colon wall (Figure 1).

Aspirin was stopped because of bloody diarrhea. Stool studies were positive for leucocytes but negative for clostridium-difficile toxin. The patient had no signs of systemic sepsis. On the second day patient became febrile, tachycardic with heart rate of 101 beat/minute and WBC elevated to 17 x 10/mm. Treatment with Ceftriaxone and Metronidazole was started. Four days later, the patient was afebrile, PR 115 beat/minute, BP 137/80 mm Hg, WBC 21.1 x 10/mm, HGB 14.9 gm/dL and platelet count 363 x 10/mm, and at this time oral vancomycin was added. Flexible sigmoidoscopy showed severe proctitis and sigmoiditis (Figure 2).

Histological examination revealed diffuse chronic active colitis in the form of severe acute cryptitis and numerous crypt abscesses with associated foci of glandular destruction and chronic changes consistent with ulcerative colitis (Figure 3). No granulomas or dysplasia were identified. Treatment with Mesalamine and Prednisone was started.

On day nine, our patient continued to have frequent bowel motions, without blood. Labs were WBC count 14.5 x 10/mm, HGB 12.6 g/dL, platelet count 415 x 10/mm and ESR 17 mm/HR. A few hours later the patient developed sudden bilateral blurred vision associated with headache. These symptoms improved within hours but did not resolve completely. Later on, he developed confusion and dysmetria
that gradually resolved. A CT scan of his head showed left posterior cerebral artery infarct and left cerebellar hemispheric infarct (Figure 4).

Ultrasound of carotid arteries and Echocardiogram were within normal limits. Hypercoagulability workup, including PTT PT/INR, anticardiolipin, homocystine, protein S and C, antithrombin III, factor V Leiden, and prothrombin gene mutation, were all within normal limits. Antinuclear antibody (ANA) was also within normal limits. Diarrhea and abdominal pain resolved, and the patient was discharged to a short-term rehab center; mesalamine was maintained, and the patient was started on a prednisone taper.

DISCUSSION

We report a case of ischemic stroke at the time of diagnosis of Ulcerative Colitis in a 48-year-old male. There are multiple mechanisms behind TE with IBD, which include platelet abnormalities, hypercoagulable state of acute systemic inflammation, hyperhomocysteinemia, and autoimmune process. Understanding these associations may influence the short- and long-term management and thromboembolism prevention in patients with IBD.

It is well recognized that IBD, like any other inflammatory process, is a hypercoagulable state associated with increased fibrinogen level and factor VIII activity, thrombocytosis and shortened PTT. Although the degree of inflammation of IBD is comparable to rheumatoid arthritis, IBD is associated with more TE than rheumatoid arthritis. A study by Mieshler, et al., showed that IBD had a higher risk of thromboembolism compared to rheumatoid arthritis and celiac disease, which is suggestive that there is more than just systemic inflammatory state behind this phenomenon. This also holds true in our case as the patient’s systemic inflammation markers were trending down, including fever, ESR, and WBC.

Platelets abnormalities/dysfunction is the second potential mechanism for the increased incidence of arterial and venous thromboembolism in patients with IBD. Patients with IBD have abnormal platelet activity, which is not correlated to disease activity. In one study, more than 30 percent of patients with IBD have reproducible spontaneous platelet aggregation, another 19 percent of patients with IBD showed hypersensitivity of platelets to low concentrations of aggregating agents, but platelets life span study was normal.

There is also increased thromboxane synthase expression in lamina propria cells that occurs in active inflammatory bowel disease, which contributes to mucosal inflammation and intramucosal thrombogenesis. One study showed that plasma levels of thromboxane B2 and beta thromboglobulin were significantly higher than controls.

Hyperhomocysteinemia associated with IBD is another potential contributing mechanism behind the increase incidence of arterial TE in patients with IBD. It was found that the median of homocysteine levels in patients with UC is similar to those in controls, but the prevalence of hyperhomocysteinemia was higher in UC than in controls. This fact is related to folate and B12 deficiency or at least lower serum values.

Although there is clear evidence of an association between IBD activity and TE, this high homocysteine level is not related to disease activity. It was also found that patients with UC are at more risk of vitamin deficiency irrespective of disease activity. Levels of homocysteine do not change even when the disease is in remission. This indicates that dietary factor/inadequate intake is the contributing factor in folate deficiency in a patient with UC, rather than increased demand with increased activity. Therefore, although hyperhomocysteinemia has an important association with IBD, it is not enough to explain the increased incidence of TE with UC relapses. In our case, the homocysteine level was checked and was within normal limits.

Autoimmunity and vasculitis can also contribute to this increased incidence of TE in patients with IBD. There were reported cases of vasculitis and strokes in patients with IBD. There was also a case report of Takayasu arteritis, complicated by stroke in a patient with UC.
Our patient had negative anticardiolipin antibody, ESR was 17, negative ANA. Moreover, there were no clinical signs or symptoms suggestive of active vasculitis.

Inherited hyper coagulable states were also reported as a cause of strokes, though in our case protein S and C, antithrombin III, factor V leiden, prothrombin gene mutation, PTT, PT/INR were all within normal limits.

The last but not least interesting mechanism behind increased TE in patients with IBD is probable unknown circulating factors; this is supported by the association of maternal active UC with fetal infarcts.

**CONCLUSION**

TE is not an uncommon extraintestinal manifestation in a newly diagnosed IBD patient. The mechanism for the development of TE in IBD patients can be explained by a multifactorial process, including the hypercoagulable state of inflammation, platelets hyperfunction, hyperhomocysteinemia, and or autoimmunity.

Patients with high risk for thrombosis should be considered for prophylactic anticoagulation. Experimental data suggest an increase in effectiveness of LMWHs, when selectively delivered at the site of disease (oral, colonic release LMWH), avoiding the parenteral route of administration.

Another debatable point is the role of total colectomy in prevention of TE. Novotny et al. suggest colectomy in all patients with UC with an arterial TE event, while Joshi et al. do not support that.

We think further data and studies are needed in this particular field to explain and guide physicians for the use of anticoagulation, anti-platelets, and/or surgery requirement.

**References:**

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