
Cerebral Thrombosis Associated with Active Crohn's Disease

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ABSTRACT. An increased incidence of cerebral thromboembolic events has been reported in young patients with inflammatory bowel disease (IBD). It has been suggested that a hypercoagulable state is associated with clinical activity of the disease, with elevation of factors V, VIII, fibrinogen and platelets and a lowering of anti-thrombin III. We present the case of a 35 y/o male with refractory Crohn's disease

who complained of headaches, blurred vision and tonic-clonic seizures. The studies demonstrated an ischemic stroke of the left cerebral hemisphere, without vascular abnormalities. Elevation of factor VIII, platelets, and antithrombin III were found. The symptoms were relieved with medical treatment and the patient has continued in good health after resection of the diseased terminal ileum.

Inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease, frequently present extraintestinal manifestations affecting nearly every organ system. Among the most common organs involved are the skin (erythema nodosum and pyoderma gangrenosum), eyes (episcleritis and uveitis), joints (peripheral arthropathy and ankylosing spondylitis), liver and the biliary tract (primary sclerosing cholangitis, fatty liver, chronic active hepatitis, cirrhosis). The nervous system may be affected indirectly, as in hypocalcemic tetany and steroid induced myopathy, and directly via the vascular system. Thromboembolic complications have been reported in IBD with an incidence ranging from 1.2% in a clinical study to 39% in autopsies (1,2). Thrombosis preferentially affects the venous compartment. Only a small fraction of all thromboembolic events involve the central nervous system.

The mechanism of procoagulant activity is unclear, but there is evidence that thrombosis at the microvascular level plays a role in the pathogenesis of IBD (3-5). We report the occurrence of an ischemic stroke in a 35 y/o male with active Crohn's disease (CD) and review the literature of cerebrovascular complications of IBD.

Case Report

A 35 y/o male with CD for four years was referred to the University Hospital for management of a refractory course of his disease. The patient had been asymptomatic using prednisone 20mg and sulfasalazine 2 gm daily, until six months prior to admission to the University Hospital, when he complained of left upper and lower abdominal pain associated with tenesmus, increased mucus in stools, flatulence and fever. He also complained of occasional headaches and dizziness. The patient visited the emergency room several times and was treated with antispasmodic medications. Two weeks prior to admission to our hospital, he developed tarry stools (five to six episodes per day). He had a hemoglobin of 4 gm/dl, was transfused with 5 units of red cells and treated with intravenous steroids. Improvement was minimal, his symptoms persisted and was referred to our institution for further management. The patient complained of headaches, dizziness, and blurred vision since four days prior to admission and had a tonic-clonic seizure. He denied nausea, vomiting, jaundice, anorexia, arthralgias, or skin lesions but he had lost 34 pounds in the past six months. The patient denied any history of other systemic illness, family history of IBD, smoking, use of alcohol or illicit drugs, prior surgeries, use of any other medications, or home remedies. He was pale, thin, acute and chronically ill, and oriented only in person. The physical examination revealed a soft and depressible abdomen, tympanic to percussion, marked tenderness to palpation over the lower abdomen, and increased bowel sounds. There was no rebound tenderness, masses, peristaltic wave or shifting

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dullness but the rectal exam showed tarry liquid stools. The patient had an apathic mood, and followed verbal but not written commands. He had comprehensive aphasia, stereoagnosia, and dysnomia. Hyperreflexia was present in all extremities, and motor strength was 4/5 throughout. The rest of the physical examination was normal. Laboratory analyses revealed hypochromic microcytic anemia with a hemoglobin of 9.1 gm/dl (14-16 gm/dl) and thrombocytosis of 615,000/mm³ (140,000-340,000/mm³). A head computerized tomographic (CT) scan showed an ischemic stroke in the left parietal cerebral hemisphere with associated edema. A head magnetic resonance image (MRI) four days later revealed a left parietal hemisphere infarction with associated cortical hemorrhage (Figure 1). A four-vessel digital subtraction

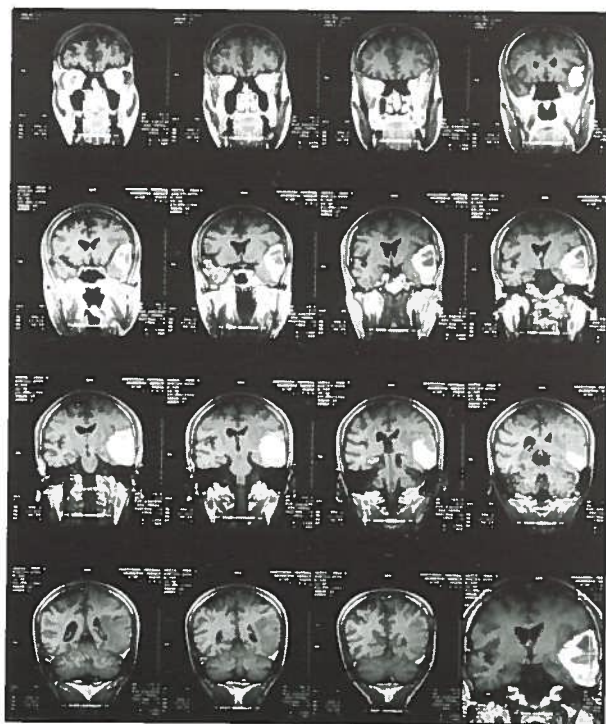


Figure 1. Head MRI showing left parietal hemispheric infarction with associated hemorrhage.

angiogram was negative for arteriovenous malformation or aneurysms. An echocardiogram revealed no thrombi and functional parameters were normal. Coagulation assesment tests showed elevated antithrombin III at 156 mg/dl (17-30mg/dl), fibrinogen of 443 mg/dl (150-350 mg/dl), and factor VIII of 251%(50-200%); normal PT (12/13), PTT (30/31), protein C: 109% (60-140%), protein S: 86% (60-140%), and factor V: 61% (60-140%). Lupus anticoagulant and antinuclear antibodies were negative. The patient was treated with steroids, anticonvulsants, measures for cerebral edema, and nutritional support. The

neurologic deficit resolved and on the 37th hospital day, an ileocecal resection was performed for a stenosing Crohn's ileitis (Figure 2). Ten months after discharge, the patient continues in clinical remission without further neurologic manifestations.

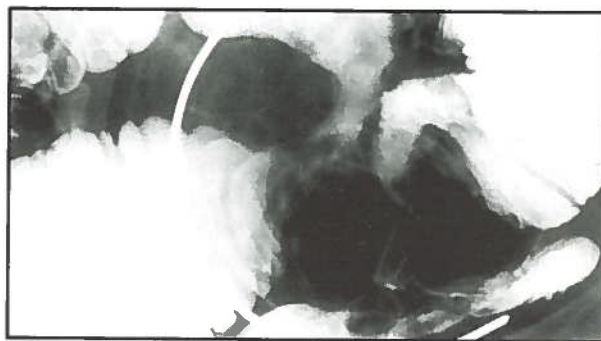


Figure 2. Small bowel series showing stenosis in terminal ileum.

Discussion

Cerebral thromboembolic disease has been associated most frequently with Crohn's disease, although a rising incidence has been reported in ulcerative colitis. The thromboembolic event is associated with exacerbation of the IBD in 64% of cases and it ranks as the third cause of death in IBD patients, after peritonitis and cancer (1, 3). The pathophysiology of the thromboembolic disease is not fully understood. Proposed mechanisms include vasculitis and hypercoagulable state (4-5). Findings that suggest hypercoagulable state are increased plasma levels of coagulation factors V, VIII, fibrinogen and fibrinopeptide A as well as thrombocytosis and spontaneous platelet aggregation (1,6-9,10-14,15). Decreased plasma levels of blood clotting activation inhibitors, such as antithrombin III, protein S (16-18), and decreased fibrinolytic activity (19-20), have been reported. Decreased factor XIII has also been observed, especially during active disease (21, 22). The presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) has also been described (23, 24). Coagulation abnormalities may be the result of inflammation and one of the pathogenic mechanisms of microscopic and macroscopic thrombosis.

Further evidence supporting hypercoagulable state is the fact that patients with inherited coagulopathies (Von Willebrand's disease and hemophilia) have a lower risk of IBD(25). Also, administration of heparin has been associated with a therapeutic effect in patients with active disease (26). Improved fibrinolytic capacity has been suggested as the main systemic, pro-thrombotic, hemostatic abnormality associated with IBD (18).

Thrombosis in IBD affects a young population, often occurs in unusual sites, and carries significant morbidity (12). Presentation may include non-specific signs and symptoms of increased intracranial pressure or focal neurologic deficit including seizures and motor deficit. The diagnosis requires a high index of suspicion and the appropriate neuro-imaging techniques, including angiography. Neurologic sequelae are proportional to the affected area, and thromboembolic events have been shown to recur with activation of disease(11)

There are no established guidelines for the management of primary cerebral venous thrombosis in IBD; anticoagulation and fibrinolytic therapy are controversial(26). Pancolectomy has no proven benefit for reversing the procoagulant process in patients with UC(20). A more conservative regime uses antiedema agents, such as steroids and mannitol, anticonvulsants, and antiplatelet therapy. Control of the active inflammatory disease must be part of the management of the thrombotic complication.

Our case illustrates the presentation of a cerebral thrombotic event in a young male with active Crohn's disease. Although unusual, this can be a life-threatening complication of IBD and must be suspected in all IBD patients with neurologic signs or symptoms.

Resumen

Se ha reportado una incidencia aumentada de eventos tromboembólicos cerebrales en pacientes con enfermedad inflamatoria del intestino. Por ello se ha sugerido un estado hipercoagulable asociado a actividad clínica de la enfermedad, con elevación de factores V, VIII, fibrinógeno y plaquetas, y disminución de anti-trombina III. En este informe presentamos el caso de un varón de 35 años con enfermedad de Crohn refractaria, que se quejó de dolor de cabeza, visión borrosa y convulsiones tónico-clónicas. Los estudios demostraron un infarto isquémico del hemisferio cerebral izquierdo, sin anomalías vasculares. Se encontró elevación de factor VIII, plaquetas y anti-trombina III. El cuadro resolvió con tratamiento médico, y el paciente ha seguido en buena salud luego de una resección del ileón terminal enfermo.

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