Journal of Current Medical Research and Opinion
Received 29-03-2024 | Revised 30-03-2024 | Accepted 19-04-2024 | Published Online 20-04-2024
DOI: https://doi.org/10.52845/CMRO/2024/7-4-20 ISSN (O) 2589-8779 | (P) 2589-8760
CMRO 07 (04), 2340-2344 (2024)
Clinical Case Reports

Cerebral Venous Thrombosis Associated with Inflammatory Bowel Diseases: Two Case Reports and Review of The Literature

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Abstract:

The risk of venous thrombosis is increased during inflammatory bowel diseases (IBD). It has been demonstrated that patients with IBD present a well-defined prethrombotic state with most often a combination of several abnormalities. Cerebral venous thrombosis (CVT) remains exceptional, then we report two cases. The first is that of a 25-year-old woman with a history of ulcerative colitis (UC) since one year, admitted for a severe flare-up accompanied by neurological signs. Magnetic resonance angiography (MRI) revealed CVT. The assessment of thrombophilia showed a deficiency in protein S and C. An anticoagulant treatment allowed a regression of the clinical and radiological manifestations. The severe attack of UC was controlled by AntiTNFα, because of the patient's corticosteroid dependence and intolerance to immunosuppressants. Thereby she remained asymptomatic for three years. The second case describes a 17-year-old patient with a history of right hemicolectomy four years ago due to Crohn's disease (CD) complicated by ileocolic stenosis. Six months later, the patient was admitted for CVT which resolved on anticoagulant, however the thrombosis reappeared a year later in the suprahepatic veins and ileofemoral veins, complicated by portal hypertension syndrome. A protein C deficiency was discovered. Anticoagulant treatment associated with the specific treatment of CD allowed a clinical and biological improvement with a follow-up of two years.

Keywords : Cerebral Venous Thrombosis, Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease, Prethrombotic State, Budd-Chiari Syndrome

Introduction:

Inflammatory bowel disease (IBD) is associated with an increased risk of thrombotic complications, particularly when the disease is in the active phase [1,2]. Cerebral venous thrombosis (CVT) is very rare in IBD. Sporadic cases and small series have been reported [1,2,4]. Their pathophysiological mechanism remains poorly understood [1,2]. We report two new cases of CVT complicating IBD in order to draw attention to this severe complication and with a review of the literature we learn to better understand the clinical, etiopathogenic, morphological and therapeutic aspects.

Case report 1:

A 25-year-old female patient, with a history of pancolitic ulcerative colitis (UC) discovered 1 year ago, under maintenance treatment with Mesalazine (2 gr oral) was admitted for mucus-bloody diarrhea (more than 10 stools/day), fever, mucocutaneous pallor in a context of deterioration in general condition. During her hospitalization, the patient presented intense headaches, associated with diplopia and motor difficulties in the left hemisphere. The neurological examination suspected damage to the VI nerve. Fundus examination revealed bilateral hemorrhagic papilledema. The brain scan was without abnormalities.

Magnetic resonance angiography (MRI angiography) showed cerebral thrombophlebitis resulting in hypersignal in the left lateral and sigmoid venous sinus as well as the vein. internal jugular at the level of the ipsilateral posterior torn hole on T1 sequences (figure 1), in T2 (figure 2, figure 3), and heterogeneous contrast enhancement at the level of the venous sinus left sigmoid and lateral with the classic delta sign, after intravenous injection of gadolinium on 3D volume acquisition in T1 sequence (figure 4, figure 5). The venous 2D TOF reconstruction image showed the absence of the signal at the level of these last two dural sinuses confirming the diagnosis of cerebral venous thrombosis (figure 6). The study of the brain parenchyma on the different sequences did not show any areas of ischemia, edema or hemorrhage. The patient received heparin therapy (low molecular weight heparin: 0.5 ml twice daily) and mannitol 20% IV infusion for 3 days with improvement neurological signs. The thrombophilia assessment revealed a deficiency of protein S at 42% (N: 65 to 140%) and protein C at 50% (N: 70 to 130%).

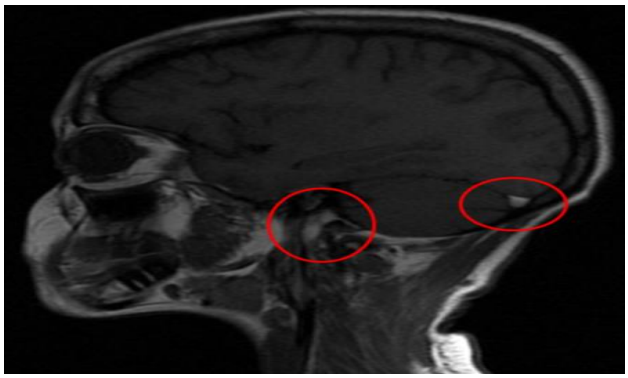

Figure 1: T1-weighted sagittal sequence, high signal at the left lateral sinus and the internal jugular vein, instead of the normal flow void low signal (thrombus).

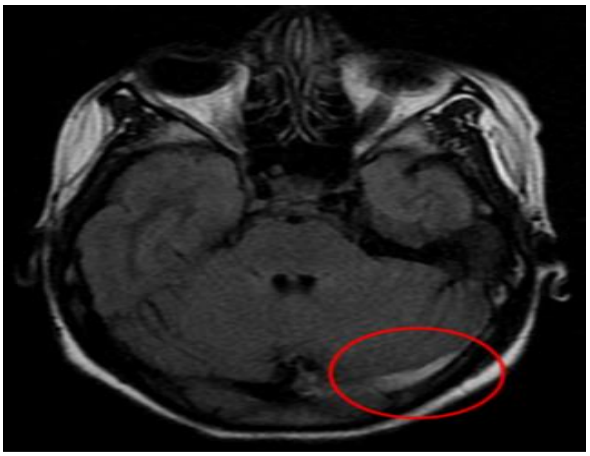

Figure 2: T2-weighted axial sequence passing through the middle cerebral fossae, shows high signal instead of the normal flow void low signal, located at the left lateral venous sinus (thrombus).

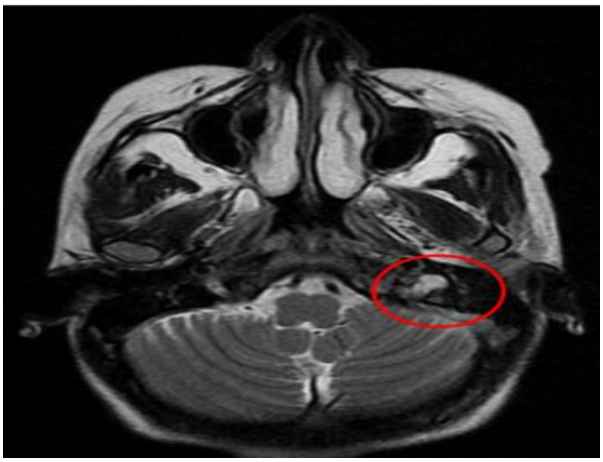

Figure 3: Axial T2-weighted sequence passing through the posterior cerebral fossa, shows high signal of the left jugular vein (thrombus).

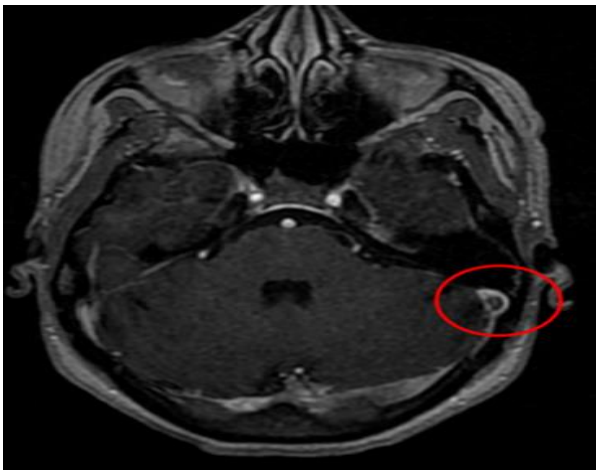

Figure 4: Axial T1-weighted image with gadolinium contrast, central low signal in the left lateral sinus corresponding to thrombosis : delta sign.

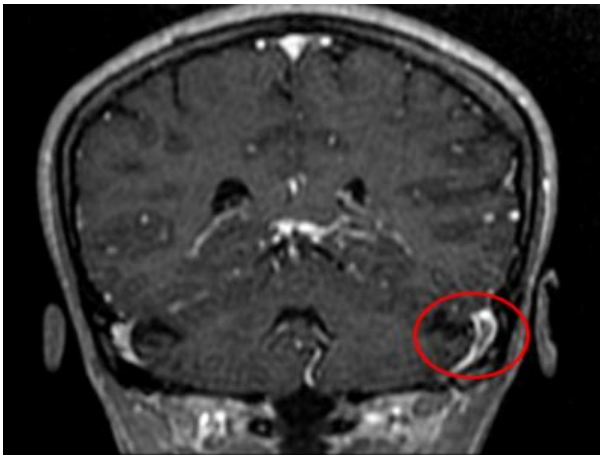

Figure 5: Frontal T1-weighted sequence with gadolinium contrast, heterogeneous signal located at the left lateral sinus (thrombosis).

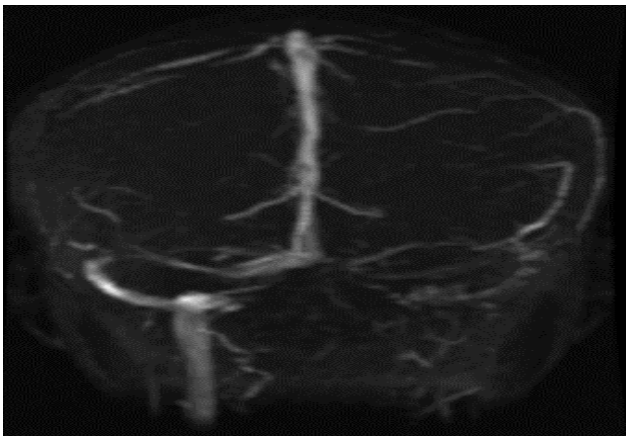

Figure 6: Venous 2D TOF reconstruction image, no flow signal of the lateral sinus, sigmoid and internal jugular vein on the left.

Given the severity of the lesions, a colonoscopy was performed on the left colon. The results revealed a diffusely blistering mucous membrane with both superficial and deep ulcerations, associated to many pseudopolyps. The flare-up was classified as severe according to the endoscopic classification (UCEIS: 10). The biological assessment revealed severe anemia with hemoglobin at 6.8 g/dl (N: 12 at 16g/dl), hyperleukocytosis with white blood cells at 12,200/mm^3 (N: 4,000 to 10,000/mm^3), a marked inflammatory syndrome with C-reactive protein at 92 mg/l (N<6mg/l) and hypoalbuminemia at 27 gr/l (N: 35 to 50g/l). The patient received intravenous corticosteroid therapy followed by oral administration combined with antibiotic therapy, blood transfusions and replacement therapy. The development was very favorable. However, the digestive signs reappeared when corticosteroid doses were reduced, which required an increase in corticosteroid doses.

Given corticosteroid dependence and intolerance to immunosuppressants, a Treatment with anti-TNFα (Infliximab: 5 mg/kg) in the attack phase (week 0.2 and 6) and maintenance phase (every 8 weeks) after a normal pre-therapeutic assessment was successfully initiated in the patient. Heparin therapy was maintained during the hospitalization period then switched to long-term vitamin K antagonists (AVK) with regular monitoring of the INR. A morphological assessment (brain scan, fundus scan and brain MRI) carried out at an interval of one month and one year after the thrombosis was normal. The patient remained asymptomatic after three years of follow-up.

Case report 2:

A 17-year-old male patient with a history of Crohn's disease (CD) for 4 years revealed by ileocolic stenosis for which he underwent a right hemicolectomy. Three months after diagnosis, he had a second surgical procedure for bowel obstruction with release of the loops, without intestinal resection. The patient remained asymptomatic with maintenance treatment based on immunosuppressants (Azathioprine at a dose of 2.5 gr/kg/day). Six months later, he was hospitalized for intense headaches associated with visual blurring, without any digestive signs. A CT scan and brain angio-MRI showed thrombosis of the left lateral venous sinus. The patient received intravenous heparin therapy for 5 days followed by AVK for 6 months, with resolution of the clinical signs and the radiological features on brain MRI. One year later, the patient was readmitted for an overall fatigue, pale skin and lower limbs painful bilateral edema.

Clinical exam showed signs of portal hypertension with moderate splenomegaly and collateral abdominal venous circulation. The biological assessment revealed severe anemia, microcytic hypochromia with hemoglobin at 7g/dl (N: 12 to 16g/dl), hypoalbuminemia at 26g/l (N: 35 to 50g/l), hypocalcemia 65mg/l (N: 82 to 106mg/l), hyponatremia 124mEq/l (N: 135 to 145 mEq/l), hypokalemia at 3mmol/l (N: 3.5 to 5mmol/l) and an

inflammatory syndrome marked with C-reactive protein (CRP) at 192 mg/l (N< 6 mg/l. The assessment of hepatic, renal and hemostasis function were correct. Doppler ultrasound revealed thrombosis of the ileofemoral veins as well as the suprahepatic veins and inferior vena cava suggesting a Budd-Chiari syndrome. The thrombophilia assessment detected a protein C deficiency isolated from 39% (N: 70 to 130%) and protein S at the lower limit of normal at 64% (N: 65 to 140%).

Endoscopy found grade 1 esophageal varices and Crohn's disease at duodenal biopsies. The colonoscopy was normal. An entero-MRI revealed mild thickening of the terminal ileum and hepatosplenomegaly. In front of this Budd-Chiari picture complicated with portal hypertension, treatment with heparin therapy at low molecular weight by subcutaneous route, relayed after 3 days by AVK was established quickly with clinical improvement. The intestinal thrust, considered moderate, was treated with corticosteroid therapy combined with replacement therapy, blood transfusions and correction of metabolic disorders. Treatment with AVK was continued for life with regular monitoring of the INR associated with maintenance treatment of Crohn's disease with Azathioprine at a dose of 2.5 g/kg/day. The evolution was marked by a general improvement with resolution of clinical and biological signs. The duplex ultrasound control 6 months later, showed a disappearance of thrombosis of the ileofemoral veins and partial repermeabilization of the suprahepatic veins and inferior vena cava. The patient is currently asymptomatic with a follow-up of 12 months.

Discussion:

The risk of venous thrombosis during IBD is well known. It is increased by a factor of 3 to 4 compared to the general population [5]. This risk is correlated with the activity of the disease, the extension of the lesions and colonic damage, particularly in cases of UC [6]. Thrombosis venous veins can be located in the lower limbs, deep abdominal veins but the cerebral location remains exceptional and unusual [6]. The mechanisms of thrombogenesis during IBD are complex and often intricate [7]. They can be either acquired (inflammation, prolonged immobilization, surgery, oral contraception, corticosteroid therapy, dehydration and hyperhomocysteinemia), or genetic (protein deficiency S and C or antithrombin III, resistance to activated protein C, Leiden mutation of factor V, anti-phospholipid antibodies, etc.) [7].

These factors are responsible for anomalies in primary hemostasis (alteration of platelets, endothelial abnormalities), coagulation (increase in pro-coagulant factors and decrease in anticoagulant factors), a hyperfibrinolysis or hyperhomocysteinemia [7]. In our patients, we noted a genetic factor represented by a deficiency in protein S and C and acquired factors favoring thrombogenesis including the concept of surgical resection and the extent of the lesions. This reinforces the hypothesis of a multifactorial origin of vascular thromboses during IBD.

The neurological signs revealing CVT are dominated by headaches, which can be isolated or associated with visual, motor or confusional disorders [8]. The confirmatory diagnosis is based on cerebral angio-MRI which remains more sensitive than CT and is currently considered like the reference examination [8]. The value of measuring D-dimer was evaluated in the diagnostic approach for CVT. Their level is most often high (>500ng/ml) when the diagnosis of CVT is confirmed except in patients with symptoms evolving since more than 3 weeks, however a normal level does not exclude the diagnosis of CVT [8]. The treatment of venous thrombosis is based on anticoagulants which must be continued for 6 months or even for life if hereditary factor identified. This treatment has proven to be very effective but recurrence of thrombosis is not preventable [8,9]. Angioplasty (with or without a stent) may be offered in cases of localized stenosis of the deep abdominal veins [10]. If these treatments remain insufficient, a transjugular intrahepatic portocaval shunt or TIPS can be implemented with excellent results [10].

Conclusion:

Cerebral venous thrombosis (CVT) is an exceptional complication during IBD but remains more formidable in cases of IBD in the active phase associated with neurological signs. The etiopathogenic mechanism is not yet elucidated but the state of hypercoagulability acquired during the course of inflammation, more or less associated with genetic risk factors could shed light on this association. Cerebral angio-MRI and assessment of thrombophilia are essential in the positive and etiological diagnosis. CVT is a serious complication, but early and well-conducted anticoagulant treatment could improve the prognosis. Moreover, we must emphasize the major benefit of prophylactic treatment of venous thrombosis in particular in cases of inflammatory activity of the disease and intestinal resections.

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