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Cerebral Infarction Associated with Crohn's Disease: A Case Report and Review of Literature

Leimin Sun[1], Piaopiao Jin[1], Zhaoqi Xu[1], Yun Qian[1] and Jianfeng Cheng[2*]

[1]Gastroenterology department, sir run runs Shaw hospital, Zhejiang University, Hangzhou 310016, China

[2]Division of Gastroenterology, Internal Medicine, University of North Carolina Charlotte Campus, Carolinas Medical Center, Charlotte, 28203, USA

Abstract

Cerebral infarction in the inflammatory bowel disease was rarely reported, especially in Crohn's disease. In this article, we report a 38-year-old male with Crohn's disease subsequently developed cerebral infarction. By reviewing the literature, we further discussed the relationship between the two diseases and seek the optimal treatment for the thromboembolisms in Crohn's disease.

Keywords: Cerebral infarction; Strokes; ThromboEmbolism (TE); Inflammatory Bowel Disease (IBD); Crohn's Disease(CD); Anti-coagulant

***Corresponding Author:** Jianfeng Cheng, Clinical Assistant Professor of Medicine, Division of Gastroenterology, Internal Medicine, University of North Carolina Charlotte Campus, Carolinas Medical Center, Charlotte, 28203, USA; Tel: (704) 355-7470; Fax: (704) 355-0770; E-mail: jiafeng.cheng@carolinashealthcare.org

Introduction

ThromboEmbolism (TE) was recognized as one of the common complications of Inflammatory Bowel Disease (IBD). Its incidence ranges from 1.2% to 3.6% in IBD and nearly 39% in autopsy [1] . Miehsler et al. declared that IBD is a risk factor for TE, which seemed to be a specific feature of IBD [2]. However, cerebral thromboembolism (arterial ischemic stroke or venous thrombosis) in Crohn's disease is quite rare. The relationship between the two diseases hasn't been quite clear so far. In most of previous cases, the mechanism of cerebral infarction in IBD may be attributed to a hypercoagulable state, prothrombotic abnormalities and the degree of inflammatory activity [3]. The case we report here not only demonstrates the mechanisms above, but also shows some new concept on the relation between atherosclerosis and Crohn's disease.

Case Report

A 38-year-old male without obvious past medical history presented to our hospital emergency room complaining of crampy abdominal pain which he rated as 10/10. No vomiting, nausea, fatigue, weight loss and other symptoms were reported. He had a 3-year history of intermittent abdominal pain and anal fistula. The later had been cured by thread-drawing therapy. He also had suffered from diarrhea for about half a year, with mushy stool 7~8 times per day. Crohn's disease was diagnosed about one month ago based on the colonoscopy and pathologic features. He was started with the mesalazine tablets 800mg three times a day. Clinical symptoms were improved until the day before admission. Urgent abdominal plain radiography showed incomplete ileus (Image A). He drank liquor 500ml per day for about 26 years and smoked 10 cigarettes a day for the same years. He denied a significant family history of Crohn's disease, but a history of hypertension and cerebral infarction of his mother.

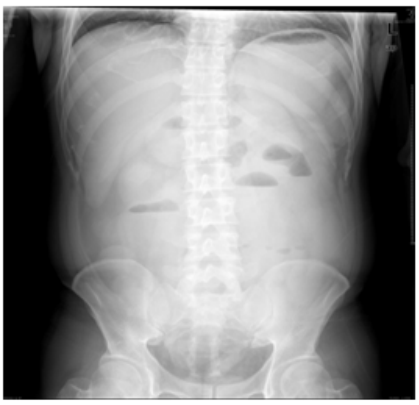

Image A: Plain abdominal radiography The appearance of multiple air-liquid interface indicated imcomplete ileus.

Physical exam: Vital signs are as the following: Temperature 36.4 centigrade; Pulse 90bpm within sinus rhythm, respiratory 18 bpm; Blood pressure: 115/81mmhg; weight /height (66kg/162cm, BMI=25.1). Epigastric tenderness was obvious, mainly on the right side. No other positive signs were found. Laboratory studies showed abnormality below (Table 1). The electrocardiogram was normal.

Table 1: laboratory data of patient on admission

Item	Result	Reference range
Blood routine examination		
White blood cells	13.6x10^9 /l ↑	4-10x1010^9 /l
Red blood cells	5.9x10^{12} /l ↑	4-5.5x10^{12} /l
Hemoglobin	16.5g/dl ↑	12-16g/dl
Platelet	279 x10^9 /l ↑	100-300 x10^9 /l
Erythrocyte sedimentation rate	18mm/hr ↑	1-15mm/hr
C-reactive protein	70.6mg/l ◄	0-5mg/l
Coagulation test		
activated partial thromboplastin time fibrinogen	53.5s ↑	28-40s
Liver function	5.57s ↑	2-4g/l
Creatinine	Normal range	
Electrolyte	Normal range	
Lipids profile	Normal range	
Serum Tri Glycerides (TGs) level as		
Very Low Density Lipoprotein (VLDL)	1.58	0.34-1.69mmol/l
Low-Density Lipoprotein (LDL),	0.92 ↑	<0.78mmol/l
High-Density Lipoprotein (HDL)	2.48	<3.36mmol/l
lipoprotein(a)	0.82 ↓	0.83-1.97mmol/l
Autoimmune profile	12	<30mg/dl
Tumor marker	Negative	
Fecal examination	Negative	
Bloody		
Red blood cell	Negative	Negative
White blood cell	5-10	0-2
Fecal occult	1-2	Negative
Stool culture	3+	
	Negative	

MR Enterography demonstrated wall thickening and enhancement of the ascending colon and ileum, enlarged nodes, and involvement of perivisceral fat (Image B).

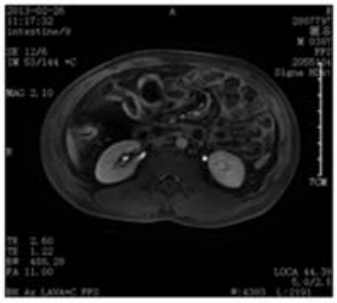

Figure 1

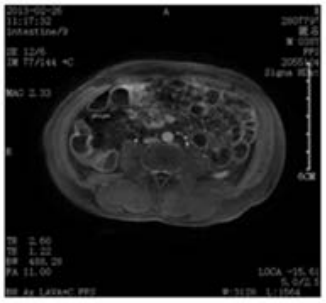

Figure 2

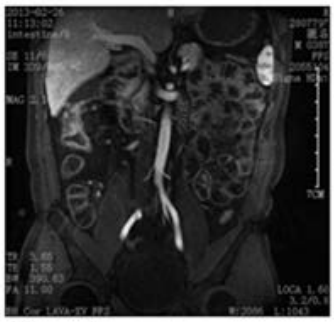

Figure 3

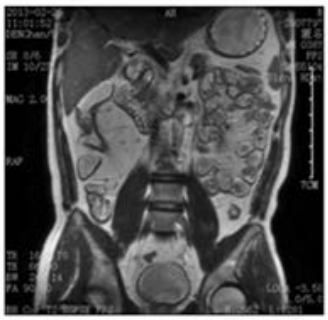

Figure 4

Image B: Magnetic resonance enterography Figure1 indicate an edema of intestinal wall; Figure 2 indicate mesenteric vascular disorders; Figure 3 and Figure 4 indicate stenosis of intestine, mainly located in the ascending colon and the ileum

We made a diagnosis of moderate active phase of Crohn's disease ($A_2L_3B_2$) according to the modified Montreal classification [4]. He was NPO and given antibiotics intravenously. We adjusted the dose of mesalazine tablets to the 1.0g, qid. Soon the pain was relieved. White blood cell and ESR dropped to normal. But he still had diarrhea for 10 to 20 times per day and CRP continued to rise (98.8mg/l).

On the third day after admission, he began to complain of the numbness of his right limbs which was failed to perform some fine movement. Neurologic evaluation showed the myodynamia declined and the sensation of the right side extremities to pain was absent; Babinski was suspected to be positive. Other significant sign was not found. Mecobalamin was given without any effect. The brain Magnetic Resonance Imaging (MRI) was arranged. Meantime, we added the oral prednisone to the regimen with a dose of 50mg per day (30mg in the morning; 20mg in the lunch), considering the CD was still active. Later, MRI revealed a new infarction of the left thalamus (Image C). Complete workup for stroke was performed. Blood rheology examination was taken and showed the increased blood viscosity (Table 2). The carotid artery ultrasound showed that the left carotid artery intima was coarse. Cardiac thrombus and valve abnormalities were excluded by Trans Esophageal Echocardiography (TEE). Cranial MRA showed no evidence of vascular malformation, occlusion, hemangioma and vasculitis of great vessels. It is most likely to be the athrosclerosis, so patient was given aspirin 100mg, qd.

Image C:

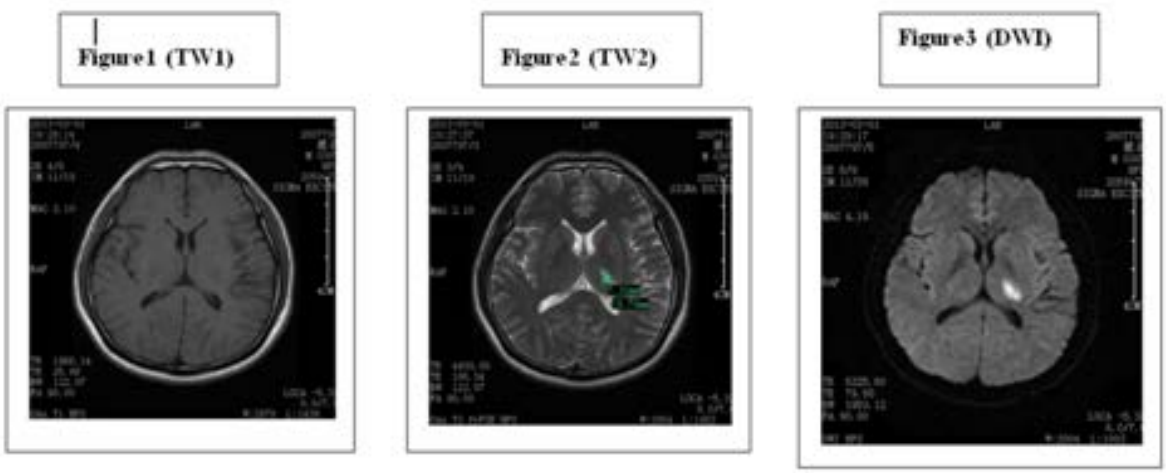

Image C: Cranial magnetic resonance: Figure 2 (T2-weighted) and Figure 3(diffusion weighted) reveals a focal high signal intensity change (19.78*7.32mm),suggesting a fresh lesions of infarction in left thalamus

Table 2: Blood rheology examination

Item	Result	Reference range
Whole blood low-shear viscosity (1/S)	13.88	11.66-21.25m Pa/S
Whole blood low-shear viscosity (5/S)	7.72	5.73-9.48 Pa/S
Whole blood low-shear viscosity (30/S)	5.41	3.56-5.55mPa/S
Whole blood low-shear viscosity (200/S)	4.55	↑ 2.74-4.23mPa/S
Whole blood viscosity	1.22	1.17-1.44 mPa/S
Whole blood high-shear relative index	3. 73	↑ 2.12-3.18
Whole blood low-shear relative index	11.37	9.00-15.76 ↓
Red cell assembling index	3.05	3.66-6.04
Casson Viscosity	4.05	↑ 2.25-3.49 mPa/S

Discussion

Crhon's Disease (CD) and Ulcerative Colitis (UC) are two main components of the Inflammatory Bowel Disease (IBD). Crohn's Disease (CD) is a relapsing bowel disease involving the whole digestive tract with a transmural pattern of inflammation. Most of the time, intestinal manifestation may be the chief complaint (like recurrent abdominal pain, diarrhea, constipation, fever, fatigue, weight loss, anemia etc.) [5].Some patients may present extra intestinal complications as initial symptoms. Vascular is also a common organ involved [6]. Study demonstrated that thromboembolic events were 2-4 fold more likely in IBD than in the healthy; active IBD might increase the relative risk even up to 15-fold [7]; the younger are more likely to happen [8,9]. Peripheral and pulmonary vessels embolism are mostly reported, while cerebral infarction is rare in IBD, occurring in only 0.12%-4% [10]. It's even less in Crohn's disease. Only a small amount of case reports were found when we review the literature. Hypercoagulable state, prothrombotic abnormalities and vascularitis are usually used to demonstrate the relationship between Crohn's disease and cerebral stroke. In inflammatory bowel disease, multi-factor contribute to the alteration of the hemodynamics :(a) Balance between coagulation and anticoagulation is often disturbed (blood coagulation factors or fibrinogen are activated; protein C, protein S, or antithrombin-III (AT-III) are deficient) [11]. (b) Some acquired and inherited reasons (heterozygote's for factor V Leiden, prothrombin 20210 variant , homozygous C677T mutation in the methylenetetrahydrofolate reductase gene) may induce the prothrombotic abnormalities [12].(c) Platelet activation occurs in most of the CD patients, which is the key reason why these patients often have an elevated platelet count [3]. Consequently, the platelet may aggregate and form a clot.(d) Hyperhomocysteinemia, due to the mal absorption of VitB12,B6 or folate secondary to the bowel inflammation (especially in terminal ileum) is also known to predispose to thrombosis of both vein and artery [3,13] and the arthrosclerosis of the vascular endothelium. (e) Crohn's disease is chronic inflammation with unclear etiology. In most cases, immune and genetic disorders were suspected to play a vital role in the pathogenesis. Cytokines like TNF-a, IL-1, von Willebrand's factor, and plasminogen activator inhibitor–1 may affect the coagulation cascade and platelet function [3].

Except for the mechanisms above, the transformation of structure of the artery in CD should also be recognized. Lafitte, et al. [14] and Richard, et al. [15] reported 1 and 2 cases respectively in 2009 and 2013.Both of them suspected that Crohn' s disease may predispose the atherosclerosis and the loss of plaque was likely to cause systemic thrombosis, including the cardiovascular and the cerebral event. By measuring flow mediated dilatation of the brachial artery and Intima Media Thickness (IMT) and Soluble CD40 ligand levels, Kayahan [16] suggested that IBD patients had an increased risk of early atherosclerosis than healthy controls, which conformed to the

former study by Papa, A. [13].In addition, arthrosclerosis is intimately interlaced the inflammation while CD is suspected to be an immune-mediated granulomatous inflammation in susceptible host. Therefore, people with CD may have a high risk for artherosclerosis because of immune-mediate endothelium dysfunction [16], lipoprotein metabolism impairment [17], and some immune associated inflammatory factors.

Based on the mechanisms above, it seems easy to clarify the ischemic stroke happened in this patient. Abnormality of his coagulation study and blood rheology examination support hypercoagulable state. Unfortunately, the coagulant and anticoagulant factors and genetic aberrant mentioned above were not examined. Although his platelet count and homocysteine were normal, his VLDL was elevated and HDL was slightly decreased. The carotid artery ultrasound showed a coarse left carotid artery intima. These results may suggest a subclinical artherosclerosis. Furthermore, he is an obese smoker and history of family history of stroke from his mother; all were the independent risk factors for stroke [18]. Finally, his active underlying disease intensified the hypercoagulable state by immune factors and dehydration. As the ischemic stroke occurred in the process of treatment, neurological side effect of each drug used should be ruled out. Our regimen comprised of antibiotics (cefotaxime, levofloxacin, and metronidazole), mesalazine, prednisone and intestinal flora regulator. None of these drugs has been reported to be associated with the hyper coagulability except the glucocorticoid in the previous literature. But prednisone was added after the neurological symptom and theoretically, its ability to reduce inflammation and tissue damage may offset the prothrombotic risks [18].

Apparently, patients with IBD are at high risk of thromboembolic events and, accordingly, should receive prophylactic intervention [3]. Currently, the therapy for this severe complication is inadequate. In several case reports [19], thrombolytic therapy, anticoagulant therapy like heparin and warfarin were used and seemed to be effective. Zitomersky, N L in [18] proposed in his review that heparin may benefit IBD patients not only as a safe anticoagulant, but also improve the colitis symptom. However, it takes a high risk of hemorrhage, as most of IBD patients have vulnerable intestinal mucus and severe bloody stools. Therefore, the anticoagulant medicine should be combined with mesalazine, steroids, immuno suppressors which help to manage these patients. In this patient, no cardio embolic and dissection causes were found. We consider it was most likely to be the arterial ischemic stroke, so we added the low-dose aspirin [18] and Lipitor to his regimen after the hemorrhage risk was fully informed. He was continued on oral prednisone. A few days later, his symptoms from Crohn's disease were well controlled. ESR, CRP, white blood cell returned to normal and he was discharged. But we still need to keep alert on the NSAIDS-associated colitis, and relapse of classic inflammatory bowel disease and serious complications of diverticular disease (fistula and perforation) [20], since his last stool OB was still strongly positive. Two weeks after discharge, he came back for the follow up. Fortunately, he recovered well and had non-bloody formed bowel movements twice a day without diarrhea or abdominal pain. His prednisone was tapered to 45mg with continuous tapering.

From this case, we learn to raise our vigilance of this severe but uncommon complication of Crohn's disease and take seriously of the neurological complaint of IBD patient. As for the treatment, there is a great need of RCT to elucidate when anticoagulant drugs could be used and how to balance the anticoagulant and hemorrhage.

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