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One case report of ischemic colitis induced by platelet-raising capsule

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Abstract

BACKGROUND

Ischemic Colitis (IC) is also known as colon ischemia (CI), which is due to colon vascular occlusion or non-occlusion reasons, resulting in reduced blood supply of colon, which is not significant enough to maintain the metabolic function of cells, leading to intestinal wall ischemia [1]. Its main symptoms include abdominal pain, diarrhea, bloody stool and so on.In severe cases, intestinal gangrene, peritonitis, intestinal stenosis and even intestinal obstruction may occur [2,3]. IC induced by long-term use of certain special drugs is relatively rare in clinical practice. This article provides the clinical diagnosis and treatment of a typical case, and also provides a new treatment idea for the treatment of ischemic colitis.

CASE SUMMARY

The patient was admitted to hospital with "abdominal pain for half a month, and mucous pus bloody stool for 3 days " ,and was diagnosed as "ischemic colitis".Symptomatic and supportive treatment such as antibiotic (levofloxacin), acid inhibition and stomach protection, fluid replenishment, and intravenous nutrition were given.The patient's colonic ulcer was considered to be related to oral administration of platelet-raising capsules, and the platelet-raising drugs were asked to be stopped for

selective review of colonoscopy,and antibiotics and mesalazine enteric-coated tablets should be stopped.Under the guidance of hematology consultation,methylprednisolone 60mg was given in combination with platelet infusion to promote platelet level.After treatment, the patient's condition was stable, stool turned yellow, symptoms improved, and he was allowed to leave the hospital.

CONCLUSION

Platelet-raising capsule can lead to IC, so clinicians should have a full understanding of the application of the drug in the treatment of various causes of thrombocytopenia, weigh the advantages and disadvantages, and observe closely.

Key Words: platelet-raising capsule; ischemic colitis; drug-related; colonic ulcer; case report

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Core Tip: The ischemic colitis caused by platelet-raising capsule is relatively rare in clinic. We reported the clinical diagnosis and treatment of a patient with IC caused by the use of platelet-raising capsule, and summarize the clinical diagnosis and treatment characteristics of these patients by reviewing the relevant literature.

INTRODUCTION

Ischemic Colitis (IC) is also known as colon ischemia (CI), which is due to colon vascular occlusion or non-occlusion reasons, resulting in reduced blood supply of colon, which is not significant enough to maintain the metabolic function of cells, leading to intestinal wall ischemia [1]. Its main symptoms include abdominal pain, diarrhea, bloody stool and so on.In severe cases, intestinal gangrene, peritonitis, intestinal stenosis and even intestinal obstruction may occur [2,3]. The pathogenesis of the disease has not been

extensively studied, but increased clotting ability has been recognized as an important factor in the pathogenesis of IC [23].Elderly people over 60 years old (especially women), and suffering from certain underlying diseases, such as cardiovascular and cerebrovascular diseases, diabetes, shock, etc, are the most prone to colon IC.The lesions can involve any segment of the colon, among which the left half of the colon such as sigmoid colon, descending colon and spleen region is the most common site of the lesions. This is because the splenic region to the sigmoid colon is the "watershed region" of colonic blood supply, where the vascular dysplasia may easily cause ischemia. In addition,the left half of the colon is supplied by the inferior mesenteric artery , which is at an acute Angle with the abdominal aorta, which also affects blood perfusion. The rectum is supplied by both the inferior mesenteric artery and the rectal artery, and ischemia is rare.Therefore, IC lesions are mainly in the left colon, and most of them are of the first pass type. The disease is relatively mild and cured after conservative medical treatment, so the prognosis is favorable [4,5,6]. Once ischemia is improved, the condition can be recovered in a relatively short time, which can be distinguished from other types of enteritis[4,5,6], such as infectious colitis, inflammatory bowel disease, pseudomembranous enteritis, diverticulitis, colon cancer, acute mesenteric ischemia, *etc*. Clinically, ischemic colitis can be divided into gangrene and non-gangrene. The latter can also be subdivided into transient and chronic types.

The treatment of IC usually includes fasting, gastrointestinal decompression, intravenous nutritional support, improved circulation, fluid resuscitation, empirical use of antibiotics and other symptomatic supportive treatment, and attention should be paid to the treatment of the primary disease. Most patients will present improvements of clinical symptoms within 1 to 2 days, and patients with complications may require surgery. However, IC induced by long-term use of certain special drugs is relatively rare in clinical practice. This article provides the clinical diagnosis and treatment of a typical case, and also provides a new treatment idea for the treatment of ischemic colitis.

CASE PRESENTATION

Chief complaints

Abdominal pain for half a month, and mucous pus bloody stool for 3 days

History of present illness

Half a month ago, the patient had abdominal pain, mainly located in the lower abdomen, which was paroxysmal. Abdominal pain was felt before stool and relieved after stool. The stool was yellow and loose, 7 times a day. Twelve days ago, the patient went to the outpatient department of our hospital for further diagnosis and treatment, and was treated with oral "cefixime". The frequency of stool was reduced to 2 times per day, and the abdominal pain was not significantly improved. Three days ago, the patient developed mucous pus and bloody stool, 2-3 times a day, and still had paroxysmal abdominal pain, no nausea, vomiting, acid reflux, heartburn, fear of cold, fever, arthralgia, dry mouth, dry eyes. He went to the outpatient department of our hospital on June 28, 2021. Gastroenteroscopy showed chronic non-atrophic gastritis with erosion, duodenal bulbitis, and multiple colonic ulcers.(See Figure 1~5)

History of past illness

He had a history of "primary immune thrombocytopenia (ITP)" for more than 3 years, and was treated with drugs such as "caffeic acid tablets and platelet-raising capsules".3 years ago, the patient was admitted to the Department of Gastroenterology of our hospital because of "abdominal pain and blood in the stool for 12 h". The whole abdomen CT scan showed: 1. Thickening and edema of the colon wall, and possible inflammatory changes, to be furthered examined if necessary, in combination with clinical evaluation; 2.Calcification of right lobe of liver;3. Small amount of fluid in abdominal cavity. Mesenteric CTA showed: 1. No obvious abnormalities in mesenteric arteries and veins; 2. Colon wall changes, consistent with ischemic enteritis, to be interpreted within clinical context;3. Small amount of ascites? Gastroscopy showed chronic superficial gastritis. Colonoscopy showed multiple colonic ulcers pending

investigation. Colonoscopic pathology showed: 1. (descending colon) mucosal chronic inflammation with multiple ulcers; 2. (ileocecal region) mucosal chronic inflammation with ulcers; 3. (transverse colon) mucosal chronic inflammation with ulcers. Added: acid-fast staining (-). Symptomatic and supportive treatment such as hemostasis, fluid rehydration, antibiotic, improvement of blood supply and regulation of intestinal flora was given. There was no reexamination of colonoscopy after discharge.Previous "gastric polyp" excision more than 10 years. "E viral hepatitis" for 3 years, denied the history of hypertension, coronary heart disease, diabetes. Denial of tuberculosis and other infectious disease history and close contact history. Vaccination history is unknown. A history of blood transfusions. Denied trauma history. Denied any drug or food allergies.

Personal and family history

Personal history: Born in the original place, long lived in Shandong, denied the history of contact with epidemic areas, infected water, special chemicals and radiation. Denied smoking and drinking history.

Marriage and childbearing history: Married at the age of 22, with a healthy spouse and one son.

Family history: Healthy parents,1 brother and 1 sister, all healthy. Denial of genetic disease, infectious disease and similar history in the family.

Physical examination

Temperature 36.2℃ Pulse: 97 beats/min, respiratory rate 18 breath cycles/min, blood pressure 110/90 mmHg, the patient is conscious, with normal mental status, no yellow staining of sclera, no palpebral conjunctival pallor, no obvious abnormalities in cardiopulmonary physical examination,flat and soft abdomen, no abdominal varicose veins and gastrointestinal type, no tenderness, rebound pain, the liver and spleen were not touched under the ribs, no masses, negative Mofey's sign, there was no knock pain in the liver and kidney areas, no voiced mobile sounds, and bowel sounds 4 times/min. No purpura or ecchymosis.

Laboratory examinations

Total bilirubin 22.3μmol/L, direct bilirubin 7μmol/L, high-density lipoprotein cholesterol 1.99mmol/L, low-density lipoprotein cholesterol 3.57mmol/L. Blood routine +HsCRP: lymphocyte percentage 18.5%, neutrophil percentage 76.4%, platelet count 68*10^9/L.Coagulation function four +D dimer :D- dimer 0.81mg/L.PPD test was negative, antinuclear antibody was negative.

Imaging examinations

Pathology: 1. Chronic inflammation of mucosa with superficial ulceration and eosinophils infiltrating the lamina propria; 2.(in the proximal ileocecal part of the ascending colon) mucosal chronic inflammation accompanied by acute inflammation, with scattered eosinophils infiltrating the lamina propria; 3.(65cm from anus) chronic mucosal inflammation accompanied by acute inflammation and superficial ulceration, with scattered eosinophils infiltrating the lamina propria; 4. Chronic inflammation of mucosa (30cm from anus) .(2021-06-28 See Figure 12)

FINAL DIAGNOSIS

1.IC caused by platelet-raising capsule 2. Colonic ulcers 3. Colonic polyps 4. Chronic non-atrophic gastritis with erosion 5. Duodenoculitis 6. Primary immune thrombocytopenia

TREATMENT

After admission, symptomatic and supportive treatment such as antibiotic (levofloxacin), acid inhibition and stomach protection, fluid replenishment, and intravenous nutrition were given.

The cause of the patient's repeated multiple intestinal ulcer was unknown, and the pathology suggested ulcer formation with eosinophil infiltration. Eosinophilic gastroenteritis should be further ruled out, and inflammatory bowel disease and other

diseases should be further ruled out. The patient was engaged in fox breeding, so it is necessary to further exclude the possibility of special type of infection. 2021-07-03The patient still had mucous, pus and bloody stool once a day, PPD test was negative, antinuclear antibody was negative. Mesalazine enteric-coated tablets were used for anti-inflammatory treatment, and Yunnan Baiyao was given orally for hemostasis.2021-07-06The patient complained of stool 2-3 times/day, watery, with mucus, pus and blood, and no other discomfort. Blood routine review + reticulocyte count: lymphocyte percentage 11%, neutrophil percentage 83.5%, absolute lymphocyte value 0.8*10^9/L, platelet count 23*10^9/L. The platelet count of the patient was significantly low, and caffeic acid tablets and platelet raising capsules were given for platelet-raising therapy.The patient had watery stool, the number of times was increased, and oral montmorillonite powder was given to stop diarrhea.The patient had multiple intestinal ulcers. It was considered whether "primary immune thrombocytopenia" was related to intestinal ulcers.The possibility of multiple intestinal ulcers caused by ITP primary disease is unlikely to be considered in hematology consultation.2021-07-07 Our department organized discussion on this difficult cases.Department of Immunology and Rheumatology thought the patient's pathology suggested eosinophilia, which was caused by many reasons, such as eosinophil granulomatous vasculitis.This patient had normal eosinophilia, normal blood routine, lung (-), skin (-), and rheumatic diseases were not considered. Imaging Department considered the patient's CT images were not clear, intestinal filling was not good, there were no enlarged lymph nodes, no fatty infiltration, no transmural inflammation, and no specific manifestations. Pathology suggested the patient's acid-fast was negative, no specific manifestations. Department of Infection said the patient had no evidence of infection (no fever, normal blood routine, negative bacterial culture, low IGE, and uncommon parasitic infections). Chief Physician Xiuli Zuo advised the patient ITP, oral platelet capsule treatment, platelet capsule contains green Dai, will cause intestinal ulcer. Many hematological diseases are complicated with intestinal ulcers, and ITP shows immune-system related ulcers. Treatment: Stop the drug, give low dose hormone therapy. At present, the patient's

colonic ulcer was considered to be related to oral administration of platelet-raising capsules, and the platelet-raising drugs were asked to be stopped for selective review of colonoscopy,and antibiotics and mesalazine enteric-coated tablets should be stopped.Under the guidance of hematology consultation,methylprednisolone 60mg was given in combination with platelet infusion to promote platelet therapy.

2021-07-09The patient has no more blood in the stool,but pain and discomfort in the lower abdomen.Scattered hemorrhagic spots can be seen on the skin.2021-07-12The patient had no abdominal pain, abdominal distension, stool once a day, no mucus, pus or blood.Reexamination of blood routine:Absolute monocyte value 0.8*10^9/L,red blood cells 4.22*10^12/L, hemoglobin 126g/L,the mean hemoglobin concentration was 312g/L, and the platelet count was 199*10^9/L.After treatment, the patient's symptoms were relieved,no more blood in the stool and the platelet level was higher than before,hormone reduction to 40mg qd.2021-07-14 Reexamination of blood routine: platelet count 230*10^9/L. The platelet level of the patient increased significantly after hormone treatment. No hematochezia was found after discontinuation of the platelet-raising capsule, and the dose of hormone was reduced to 20mg qd.

OUTCOME AND FOLLOW-UP

2021-07-19 Review colonoscopy: colonic ulcer; Endoscopic forceps removal of colonic polyps.(See Figure 6~8) Endoscopic biopsy showed: 1. Tubular adenoma (50cm from anal margin); 2. Acute and chronic inflammation of mucosa with erosion (proximal ileocecal part of ascending colon).(See Figure 13)Re-examination colonoscopy of the patient showed significant improvement of colonic ulcer, which was considered to be associated with platelet-raising capsule.The patient's symptoms improved after symptomatic treatment such as acid inhibition, nutritional support, hemostasis, platelet infusion, and hormone, and the platelet level was higher than before. The patient could be discharged .The patient was told to recheck blood routine and coagulation function 3 days after discharge, make sure to return to the hematology department, adjust hormone dosage under the guidance of specialists, and do not reduce or stop the

medication by himself; Pay attention to the change of stool color, review gastroenteroscopy regularly, and follow up on discomfort.

After discharge, the patient did not take platelet-raising capsule again, and did not have abdominal pain, diarrhea, blood in the stool and other symptoms.2022-08-01 Review colonoscopy of the patient in our hospital showed no obvious abnormalities.(See Figure 9~11)

DISCUSSION

The onset of this case was acute, with abdominal pain, diarrhea, and then hematochezia. Colonoscopy shows multiple ulcers in the colon.The clinical symptoms improved rapidly after the discontinuation of the platelet-raising capsule, while continued use of the drug will lead to worsening of the disease. The patient had a similar history 3 years ago, and whole-abdominal CT showed thickening and edema of the colon wall. Inflammatory changes were considered. Mesenteric CTA showed 1, no obvious abnormality in mesenteric arteries and veins 2, changes in colon and intestinal wall, consistent with ischemic enteritis. Colonoscopy shows multiple ulcers in the colon. It was reported that ischemic colitis occurred in patients vaccinated with the second dose of COVID-19 inactivated vaccine [22]. The patient presented abdominal pain after vaccine injection. It was considered whether it was related to vaccination.However, the patient had a similar medical history 3 years ago, and the clinical symptoms improved rapidly after the discontinuation of the platelet-raising capsule this time, and he did not take platelet-raising capsule again after discharge.Reexamination by colonoscopy in our hospital on 2022-08-01 showed no obvious abnormalities. Considering the above factors, the diagnosis of IC caused by platelet-raising capsule was established.

Drug-related IC is a disease that occurs due to the use of disease-causing drugs, and whose clinical symptoms and auxiliary findings are consistent with the characteristics of ischemic lesions in the colon. [20] Clinical symptoms can be rapidly improved after discontinuation of pathogenic drugs, while continuous use of the drug will lead to continuous progression of the disease, which is a unique clinical feature of

drug-related IC.Recent studies have found that the incidence of right colon lesions in drug-related IC is higher than that in IC[7]. Thus, drug-related IC may have a higher incidence of general abdominal pain or right abdominal pain than IC, which primarily occurs on the left side.

In terms of diagnosis, laboratory tests showed elevated peripheral white blood cells, decreased hemoglobin to varying degrees, elevated blood amylase, elevated D-dimer, elevated lactate dehydrogenase, and decreased serum HCO3- level. There should be stool cultures of Salmonella, Campylobacter Shigae and Escherichia, the latter of which has been implicated in causing colon ischemia; parasitic or viral infections such as cytomegalovirus should also be ruled out. [23]Plain abdominal radiographs may have nonspecific findings, such as thumb marks, inflatable rings, thickening of the intestinal wall, and intestinal failure, which is an effective method to rule out colon infarction and intestinal perforation.Abdominal CT can indicate the location of the diseased intestinal segment and the extent of involvement, and can also find complications such as concomitant disease and perforation. The main manifestations are intestinal wall thickening, blurring of the periintestinal fat space, and occasional intestinal wall gas. [21] CT angiography is of little significance in the diagnosis of IC, because IC is non-occlusive and transient ischemic injury of small vessels.Because it cannot show tertiary blood vessels, it is of little clinical significance.Colonoscopy is considered as the gold standard for the diagnosis of IC. Under the microscope, it showed intestinal mucosal congestion, edema, ecchymosis, submucosal bleeding, the mucosa was dark red, the vascular network disappeared, and some mucosal necrosis, followed by mucosal detachment and ulcer formation. The boundary between the lesion site and the normal intestinal segment was clear. Under the microscope, the bleeding nodules were the characteristic manifestations of IC, caused by submucosal bleeding or edema. [21]Colonoscopy should be avoided when patients show signs of peritonitis; When the endoscopist finds gangrene, he/she should directly terminate the colonoscopy and perform emergency surgery [9].The histopathological features showed a large number of fibrinous thrombus and hemosiderin-containing cells in the

submucosa.Compared with IC, the incidence of eosinophilic infiltration in drug-related IC is higher ,the incidence of ulcers and necrosis is lower.

The patient took oral platelet-raising capsule to treat ITP. According to traditional Chinese medicine, blood stasis, blood heat and Qi deficiency are the main causes of ITP. Clearing heat and cooling blood and promoting blood stasis are the main principles for treating this disease. It has the effect of clearing heat and detoxifying, dispersing stasis and eliminating spots, cooling blood and stopping bleeding. The main drug of platelet-raising capsule is indigo naturalis, a pigment processed from the stems and leaves of Indigo, persicaria tinctoria, and indigotica tinctoria. Its main ingredients are indigo and indirubin. Modern pharmacological studies show that the active components of indigo,indirubin and indigo can effectively inhibit the activity of bacteria and regulate the immune function of the organism. Peel, forsythia can be anti-inflammatory, antibacterial, reduce capillary permeability, inhibit the allergic reaction of the body. Studies have pointed out that platelet-raising capsule can not only reduce inflammation, inhibit bacteria and regulate the body's immune function, but also promote the level of PLT and improve the coagulation function. Studies [10,11] have shown that traditional Chinese medicine containing indigo naturalis components (such as Compound Qingdai Pill and platelet-raising capsule) can cause IC.The pathogenesis of IC induced by indigo naturalis may be related to the following factors: (1)indigo naturalis stimulates colon mucosa and damages colon mucosa; (2) indigo naturalis can cause diarrhea, and severe diarrhea can lead to reduced systemic effective circulating blood volume, increased intestinal pressure, vasospasm, etc, resulting in insufficient blood supply to the colon wall; (3)indigo naturalis has the effect of cooling blood and stopping bleeding, and has obvious procoagulant effect, which can lead to intravascular cellulose thrombosis, blocking blood vessels,and thus cause ischemic necrosis of colonic mucosa. [10-13] Elderly patients may have the basis of intestinal arteriosclerosis themselves, and the use of Qingdai is more likely to induce ischemic lesions. [12]

ITP-induced bleeding refers to thrombocytopenia in the peripheral blood, resulting in skin, mucosa, and even internal bleeding, but the tendency of spontaneous bleeding

usually occurs when the platelet is lower than 20 ×10^9/L.The gastrointestinal bleeding of this patient was not accompanied by skin petechiae and ecchymosis, which was inconsistent with the clinical characteristics of intestinal bleeding caused by ITP. In addition, the patient had blood in the stool when taking Chinese medicine containing Qingdai, and the symptoms improved and did not recur after stopping the drug, suggesting that the patient's digestive tract lesions were closely related to the use of drugs. However, it remains to be studied whether patients with ITP-based lesions have synergistic effects with Qingdai to further increase the risk of intestinal ischemia.

When patients develop drug-induced IC, disease-causing drugs should be stopped immediately and use similar treatment to other causes of IC[8,14]. The treatment of IC is related to the severity of the patient's condition [1,15]. For severe patients, intravenous infusion, optimal hemodynamic status, intestinal rest, empirical use of antibiotics and avoidance of vasoconstrictor therapy were adopted, and most patients would improve their clinical symptoms within 1 ~ 2 days. Patients with complications may need surgical intervention [14].Medical treatment: Most patients with acute mild to moderate IC can receive conservative medical treatment, including routine fasting, gastrointestinal decompression, intravenous nutritional support, fluid resuscitation, and vasoactive drugs to improve circulation, such as papaverine and salvia miltiorosa. Pay attention to and treat the primary disease early, at the same time applying symptomatic treatment. [16,17] Prophylactic anticoagulation is recommended, but therapeutic anticoagulation is not recommended. [18] In the treatment regimen, empiric intravenous infusion of broad-spectrum antibiotics covering colonic bacteria can minimize the risk of mucosal damage, bacterial translocation and even sepsis [9]. Antianaerobic antibiotics and fluoroquinolones, aminoglycosides or third-generation cephalosporins are recommended for moderate to severe IC [1].Surgical treatment is required when diffuse peritonitis, perforation, circulatory instability due to persistent bleeding, or repeated blood transfusions are required.

In conclusion, although traditional Chinese medicine containing indigo naturalis is an effective drug in the clinical treatment of ITP, patients should be reminded to

observe the symptoms of digestive tract and the characteristics of stool during application. If abdominal pain, diarrhea, and blood in the stool are present, the clinician should consider the possibility of ischemic colitis, order the patient to discontinue the drug immediately, and prescribe aggressive treatment to prevent serious complications. If a patient has had such an adverse reaction on previous medication, it is best not to use the drug again.

CONCLUSION

The patient developed IC after taking platelet-raising capsules,however, the symptoms improved rapidly after drug withdrawal and there was no recurrence during follow-up,indicating that the occurrence of IC in the patient was closely related to platelet-raising capsules. Platelet-raising capsule can lead to IC, so clinicians should have a full understanding of the application of the drug in the treatment of various causes of thrombocytopenia, weigh the advantages and disadvantages, and observe closely.Once abdominal pain, diarrhea, and blood in the stool occur, the drug should be stopped immediately, with implementation of active treatment, and avoidance of the further use the pathogenic drug.

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PRIMARY SOURCES

1	Sisi Zhou, Quan Shi, Yanfeng Zheng, Yihan Zhuang, Yiting Lin, Zeyu Huang, Jing Yu. "Sheng-Xue-Xiao-Ban Capsule–induced ischemic colitis and pulmonary embolism in an idiopathic thrombocytopenic purpura patient: a rare case report", Annals of Translational Medicine, 2022 Crossref	16 words — < 1%

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