Case Reports in Gastroenterology

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379
Received: November 16, 2021
Accepted: January 25, 2022
Published online: March 25, 2022

Case and Review

Immune Thrombocytopenic Purpura as an Extraintestinal Manifestation in a Patient with Ulcerative Colitis

Renata de Medeiros Dutra Luciana Rocha Almeida Camila Sinkos
Ana Clara Muraro Bonini Rogerio Saad-Hossne Julio Pinheiro Baima
Ligia Yukie Sassaki

Medical School, São Paulo State University (Unesp), Botucatu, Brazil

Keywords
Immune thrombocytopenic purpura · Ulcerative colitis · Inflammatory bowel disease

Abstract
Immune thrombocytopenic purpura (ITP) is characterized by the presence of autoantibodies against platelet membrane antigens, leading to immune-mediated platelet destruction. ITP is considered as a rare extraintestinal manifestation (EIM) of ulcerative colitis (UC). This report aimed to describe a rare case of UC associated with ITP and a review of the literature. A 49-year-old man was admitted to our hospital with severe acute colitis which was responsive to treatment (hydrocortisone 300 mg/day). The patient was discharged from the hospital with prednisone 60 mg/day and azathioprine 50 mg/day. During the follow-up, the dose of azathioprine was increased to 100 mg/day (1.3 mg/kg), while prednisone tapering was started. After 3 months, the patient presented with thrombocytopenia (30,000 platelets/μL) without improvement despite receiving the suspension of azathioprine; thus, a bone marrow aspirate was performed. The bone marrow analysis showed hyperplasia of the erythroid series, megaloblastosis, hyperplasia of megakaryocytes with mild dyspoiesis, and absence of cytotoxicity, a morphological finding consistent with ITP. The patient was treated with prednisone 1 mg/kg/day which resulted in partial improvement of the condition and his still being followed up as outpatient using mesalazine 3.2 g for UC and a platelet count of approximately 50,000/μL using eltrombopag. As reported, ITP is a rare EIM in patients with UC. Due to the risk of complications, such as bleeding, hematological changes in these patients should be considered. The disease should be suspected in the presence of thrombocytopenia, always excluding the side effects of medications in advance, especially immunosuppressants. The correct diagnosis

Correspondence to:
Renata de Medeiros Dutra, renatamedufpb@gmail.com

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

of this rare manifestation and proper treatment are essential to control the condition, prevent complications, and improve the patient's prognosis.

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that presents with continuous inflammation of the mucosa of the colon. It affects the rectum and colon continuously and is characterized by a course of disease remission and recurrence [1], and may present with extraintestinal manifestations (EIM). The main EIMs are arthritis and arthropathy, primary sclerosing cholangitis, metabolic bone disease, and uveitis, which are more prevalent in patients with Crohn's disease than in patients with UC [2]. Hematological manifestations are rare, with the most prevalent being coagulopathies such as pulmonary thromboembolism and deep vein thrombosis [2].

Immune thrombocytopenic purpura (ITP) is a rare EIM of IBD, commonly associated with UC [3]. ITP is characterized by the presence of autoantibodies against platelet membrane antigens, leading to immune-mediated destruction of platelets [4]. The pathogenesis of the association between IBD and ITP is explained by the mimicry between the luminal mucosa and platelet membrane antigens, leading to immunogenic activation that favors platelet destruction in the spleen [5]. The treatment of ITP includes the use of immunosuppressants such as corticosteroids, intravenous gamma globulin, or anti-D immunoglobulin, as first-line therapies [6]; however, in the association between ITP and IBD, medications that act on both diseases can be used.

Patients with IBD are at increased risk of having another associated autoimmune disease; therefore, in most cases, it is very difficult to differentiate between EIM and concomitant autoimmune disease. Given the rarity of the case and its implications for therapeutic management, we aimed to describe the case of a patient with UC who presented with ITP as a rare EIM and review the literature on the subject.

Case Report

A 49-year-old man was admitted to the emergency room in October 2019 with diarrhea for 15 days, with approximately 8 bowel movements per day, hematochezia, and abdominal pain, without improvement with the use of ciprofloxacin for 7 days. He developed hyporexia and progressive weakness and was admitted to the hospital. His family and personal history were without particularity. Colonoscopy showed an inflammatory process in the descending colon, sigmoid, and rectum, and pathological findings compatible with mildly active chronic colitis, erosions, and regenerative alterations. On admission to the emergency room, the patient presented with dehydration, skin pallor, fever, tachycardia (heart rate: 110 bpm), hypotension (blood pressure: 80/60 mm Hg), and diffuse abdominal pain without signs of peritonitis. Biochemical tests showed anemia and increased C-reactive protein levels (Table 1). Screening for Clostridium was unavailable at the time of admission. Simple abdominal radiography showed an air-fluid level and dilatation of the colon loops (shown in Fig. 1a) computed tomography scan of the abdomen showed gaseous distension of the sigmoid, with parietal thickening of the left colon and proximal rectum (shown in Fig. 2).

The patient was diagnosed with severe acute colitis, and treatment was started with volume expansion and broad-spectrum systemic antibiotic therapy using ceftriaxone 1 g IV 2

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

Table 1. Evolution of laboratory tests and patient treatment

Date	11 Oct 2019 Hospital admission	21 Oct 2019 Hospital discharge	07 Jan 2020	27 Jan 2020	20 Feb 2020	05 Mar 2020	21 May 2020	25 Jun 2020	23 Jul 2020	27 Nov 2020	20 May 2020
Hemoglobin, g/dL	10.1	10	13.6	14	12.8	12.9	14.4	14.2	14.7	10.8	14.4
Platelets, $10^3/mm^3$	396	385	30	15	20	34	45	47	21	53	40
Leukocytes, mm^3	5,800	4,300	7,900	6,100	5,800	10,400	8,600	7,600	5,900	8,400	6,100
C-reactive protein, <1 mg/dL	22.0	2.2	0.50	0.5	–	–	0.5	–	–	–	–
Medications	Ceftriaxone metronidazole Hydrocortisone	Azathioprine Prednisone 30 mg/day	Azathioprine 100 mg/day	Azathioprine 100 mg/day (suspended)	Prednisone 80 mg/day Citoneurin	Prednisone 80 mg/day Mesalazine Cytoneurin	Prednisone (tapering) Mesalazine Cytoneurin	Mesalazine	Cyclophosphamide Mesalazine	Eltrombopag mesalazine	Eltrombopag Mesalazine

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

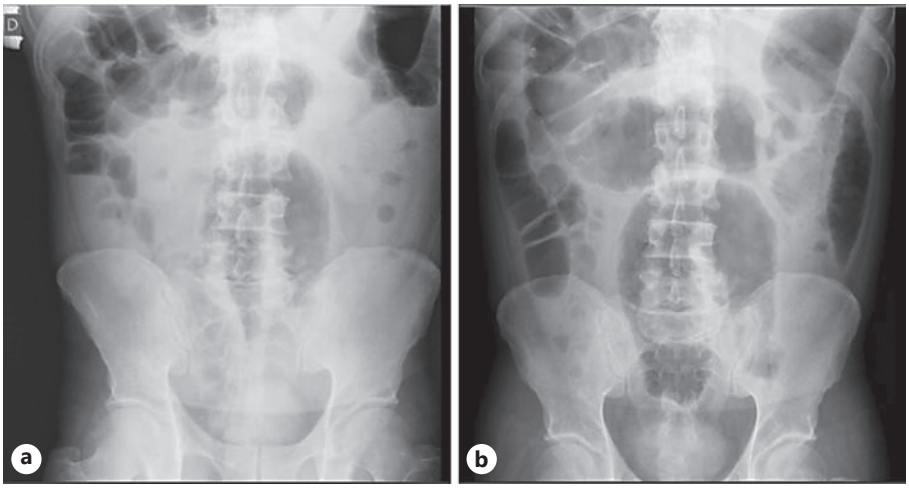

Fig. 1. Simple radiography of the abdomen at patient admission to the Emergency Room shows air-fluid level and colonic dilatation in the standing (**a**) and lying down views (**b**).

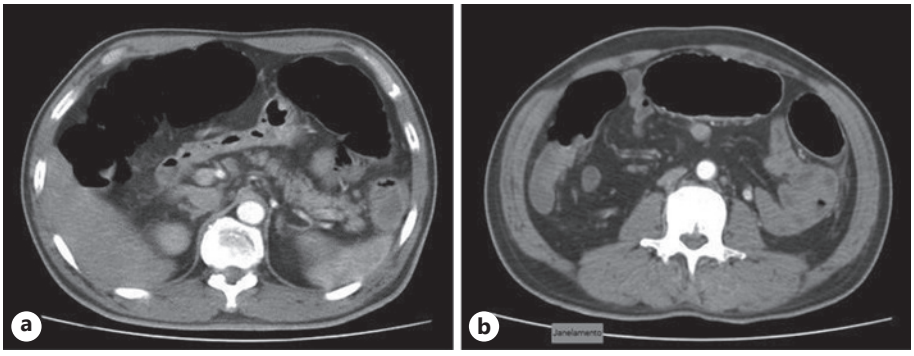

Fig. 2. a, **b** Abdominal computed tomography shows gaseous distension of the sigmoid, with parietal thickening of the left colon and proximal rectum.

times a day and metronidazole 500 mg IV 3 times a day. In addition, the patient received antiparasitic treatment with ivermectin 2 g oral single dose and albendazole 400 mg orally daily for 5 days. Intravenous hydrocortisone 100 mg 3 times a day was started for the treatment of severe acute colitis. Colonoscopy showed severe UC with the presence of erosions and deep ulcers, consistent with the Mayo 3 endoscopic score (shown in Fig. 3). Anatomopathological examination showed intense proctitis, marked plasmacytosis, epithelial reactivity and ulceration, absence of infection by opportunistic organisms, or viral cytopathic effect. The patient presented with clinical improvement, decreased evacuation frequency, absence of abdominal pain, nausea or vomiting, and improved appetite. Hydrocortisone was transitioned to oral prednisone after the fifth day of hospitalization, and azathioprine 50 mg was administered at this time. The patient was discharged from the hospital after 10 days of hospitalization with azathioprine 50 mg/day (weight 76 kg) and prednisone 60 mg/day.

The patient returned to the outpatient clinic 2 weeks after hospital discharge in November 2019, complaining of four to five episodes of loose stools a day, with the presence of blood and mucus. The dose of azathioprine was increased to 100 mg/day (1.3 mg/kg/day), and the corticosteroid was tapered to 5 mg/week. In the outpatient consultation in January 2020, thrombocytopenia (30,000 platelets) was observed, and azathioprine was discontinued due

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

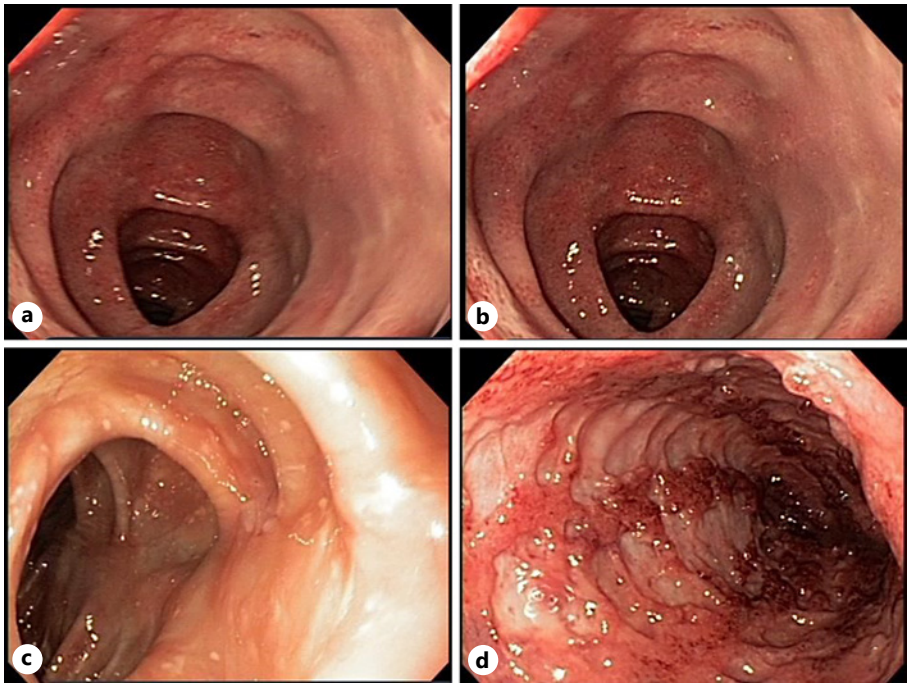

Fig. 3. Colonoscopy images show severe active UC with the presence of edema and fibrin-covered erosions in the transverse colon (**a**, **b**), sigmoid and descending (**c**), and deep ulcers in the rectum (**d**), consistent with Mayo 3 endoscopic score.

to suspicion of drug myelotoxicity. The patient was evaluated by the hematologic team and started using folic acid, thiamine, pyridoxine, and cyanocobalamin. In February 2020, the patient underwent bone marrow aspiration.

Bone marrow analysis showed hyperplasia of the erythroid series, megaloblastosis, megakaryocyte hyperplasia with mild dyspoiesis, and absence of cytotoxicity, a morphological picture compatible with ITP. The patient continued receiving prednisone at a dose of 20–80 mg/day with the maintenance of the platelet count (20,000–47,000) and received treatment with cyclophosphamide, without improvement in thrombocytopenia. In October 2020, the patient started using eltrombopag 50 mg/day, maintaining platelets between 40,000 and 60,000, without intestinal bleeding, and in clinical and endoscopic remission of the UC using mesalazine 3.2 g/day. The last colonoscopy performed in September 2020 showed mildly active UC, consistent with the Mayo 1 endoscopic score (shown in Fig. 4).

Discussion

IBD is associated with EIM, the most common being musculoskeletal (peripheral and axial arthritis), dermatological (pyoderma gangrenosum and erythema nodosum), hepatobiliary (primary sclerosing cholangitis), hematological (autoimmune anemia), and ophthalmological (episcleritis) diseases [1]. Furthermore, patients with IBD are at increased risk of presenting with other autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, and multiple sclerosis, due to the overlapping pathogenesis of autoimmune diseases [7, 8].

ITP is a disease characterized by the consumption of platelets by the immune system due to the presence of IgG-type antibodies against the platelet membrane. The disease affects

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

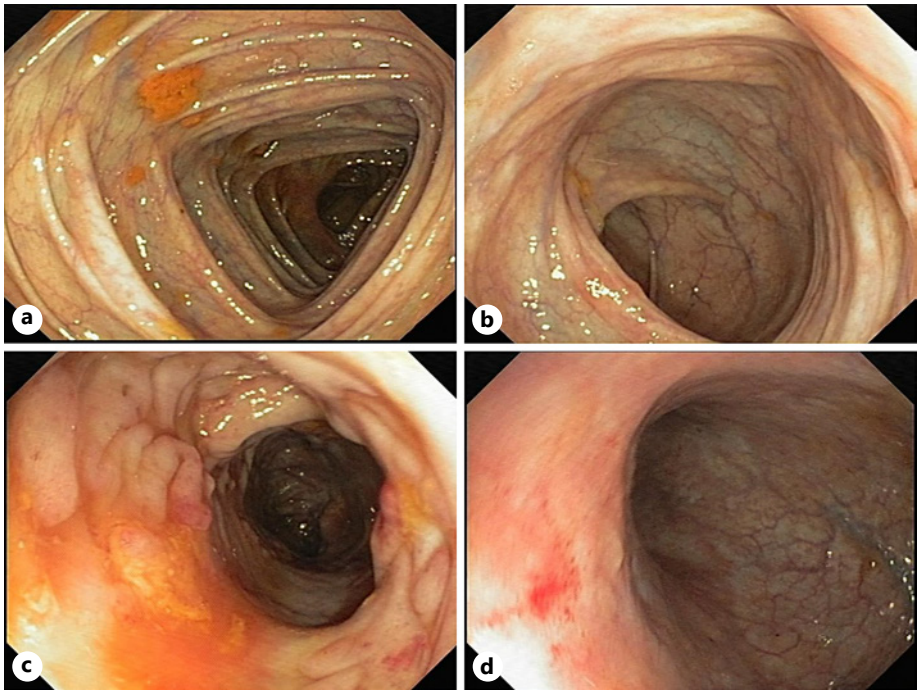

Fig. 4. Colonoscopy images show mild active UC with mucosal healing in the transverse colon (**a**, **b**), presence of edema, and mild erythema in the left colon (**c**, **d**), consistent with Mayo 1 endoscopic score.

mostly women and presents with the formation of petechiae, purpura, or cutaneous and mucous ecchymosis, in addition to isolated thrombocytopenia. The differential diagnoses include hemolytic uremic syndrome, disseminated intravascular coagulation, paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, lymphoproliferative disorders, infection (human immunodeficiency virus, hepatitis C), and thrombocytopenia induced by drugs such as alcohol and heparin [9].

ITP is considered a rare EIM in patients with UC [10], and about 40 reported cases of this association have been reported in the literature, resulting from the mimicry between platelet antigens and bacterial antigens in the intestinal lumen [5]. A systematic review published in 2020 [4], found only 12 reports on the association between Crohn's disease and ITP. Despite these reports, it is difficult to differentiate between ITP as an EIM or a different autoimmune disease associated with IBD.

The guidelines of the American Society of Hematology, 2019 [6], suggest that, for the management of ITP, corticosteroids, intravenous gamma globulin or anti-D immunoglobulin should be used as first-line therapies due to their rapid response. In patients who are steroid-dependent or refractory, eltrombopag, a thrombopoietin receptor agonist, is recommended as a treatment. Other treatments include azathioprine and cyclophosphamide, which are considered important options for refractory ITP. However, due to the lack of sufficient data, there is no formalized consensus recommendation on the use of immunosuppressants for treatment. In the association of ITP and IBD, the patient can be treated with biological therapy (rituximab and infliximab) and immunosuppressants (azathioprine), with a good response after colectomy as described in some case reports, especially in refractory patients for clinical treatment [4, 11, 12]. Rituximab is another treatment option for both entities, but the results are not conclusive, highlighting the need for further research to investigate the role of B cell lines in colonic inflammation [13].

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

Azathioprine is used as a maintenance therapeutic option in IBD and may be associated with adverse events such as myelosuppression, hepatotoxicity, and pancreatitis [1]. In the reported case, the patient presented with thrombocytopenia while using azathioprine and prednisone as therapy for UC. However, since the medullary aspirate was hypercellular and thrombocytopenia remained after the drug was discontinued, it was possible to rule out the adverse effect of the immunosuppressant as a cause of the hematological condition, which was associated with ITP secondary to UC activity, azathioprine has been considered as a trigger of ITP, and with partial response to first-line corticosteroid treatment.

IBD can progress with the development of EIM, as well as overlap with other autoimmune diseases, such as ITP. Despite reports showing options such as colectomy, it is important to highlight the good response of the present case using the second-line treatment for ITP with eltrombopag and conventional therapy with mesalazine to control UC. It is important to remember that drug reactions should always be ruled out from treatment instituted with biological therapy and immunosuppressants for IBD control.

Conclusion

ITP is a rare EIM present in patients with UC. The disease should be suspected in the presence of thrombocytopenia, always excluding the side effects of medications in advance, especially after the use of immunosuppressants.

Statement of Ethics

The study was approved by the local Research Ethics Committee of the Medical School, Botucatu (CAAE: 50971321.0.0000.5411). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare regarding the present work.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

All authors contributed to this manuscript. Renata de Medeiros Dutra, Luciana Rocha Almeida, Camila Sinkos, Ana Clara Muraro Bonini, Rogerio Saad-Hossne, Julio Pinheiro Baima, and Ligia Yukie Sassaki contributed to the conception and design of the study; the acquisition, analysis, and interpretation of data; drafting the article, revising it critically for important intellectual content and approving the final version to be submitted.

Case Rep Gastroenterol 2022;16:140–147
DOI: 10.1159/000522379

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European Evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017;11(6):649–70.
2 Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. European Crohn's and Colitis Organisation. The First European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2016 Mar;10(3):239–54.
3 Queliza K, Ihekweazu FD, Ali A, Kellermayer R. Inflammatory bowel disease and immune thrombocytopenic purpura: combined immune dysregulation in an adolescent. Ann Clin Lab Sci. 2017;47(2):226–8.
4 Epistola R, Do T, Vankina R, Wu D, Yeh J, Fleischman MW, et al. Immune thrombocytopenic purpura (itp) as an uncommon extraintestinal complication of crohn's disease: case vignette and systematic literature review. Case Rep Hematol. 2020 Mar 26;2020:20204785759.
5 Chandra S, Finn S, Obah E. Immune thrombocytopenic purpura in ulcerative colitis: a case report and systematic review. J Community Hosp Intern Med Perspect. 2014;4(2).
6 Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829–66.
7 Cohen R, Robinson D Jr, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002. Inflamm Bowel Dis. 2008;14(6):738–43.
8 Halling ML, Kjeldsen J, Knudsen T, Nielsen J, Hansen LK. Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases. World J Gastroenterol. 2017;23(33):6137–46.
9 Zainal A, Salama A, Alweis R. Immune thrombocytopenic purpura. J Community Hosp Intern Med Perspect. 2019;9(1):59–61.
10 Iwasa T, Nakamura K, Ihara E, Aso A, Ito T. The effective treatment with cyclosporine of a ulcerative colitis patient with concurrent idiopathic thrombocytopenic purpura who subsequently developed spontaneous pneumomediastinum. Intern Med. 2017;56(11):1331–7.
11 Brunet E, Martínez de Sola M, Garcia-Iglesias P, Calvet X. Immune thrombocytopenic purpura associated with Crohn's disease with complete response to infliximab. Púrpura trombocitopénica inmune asociada a enfermedad de Crohn con respuesta completa a infliximab. Gastroenterol Hepatol. 2019;42(1):37–8.
12 Negoro A, Takano T, Tajiri H, Nezu R, Kawamura N, Brooks S. A role of colectomy in immune thrombocytopenic purpura associated with ulcerative colitis: a case report and a review of the literature. Int J Colorectal Dis. 2014;29(9):1179–80.
13 Leiper K, Martin K, Ellis A, Subramanian S, Watson AJ, Christmas SE, et al. Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis. Gut. 2011;60(11):1520–6.