Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9590-22
Intern Med 62: 69-74, 2023
http://internmed.jp

【 CASE REPORT 】

Gastro-colic Fistula-associated Hypersplenism Causes Pancytopenia in a Patient with Crohn's Disease

Seisuke Saito[1], Nobuhiro Ueno[1], Yuki Kamikokura[2], Yuya Sugiyama[1], Yu Kobayashi[1], Yuki Murakami[1], Takehito Kunogi[1], Takahiro Sasaki[1], Keitaro Takahashi[1], Katsuyoshi Ando[1], Shin Kashima[1], Kentaro Moriichi[1], Hiroki Tanabe[1], Mishie Tanino[2], Toshikatsu Okumura[1] and Mikihiro Fujiya[1]

Abstract:

A 24-year-old woman was admitted to our hospital due to abdominal pain and a high fever. She was diagnosed with ileocolonic Crohn's disease (CD), complicated with a gastro-colic fistula and splenomegaly. After initial treatment with an infliximab-biosimilar, all blood cell line counts markedly decreased. Three-dimensional reconstructed computed tomography revealed splenic vein narrowing. Thus, her pancytopenia was deemed to have likely been caused by hypersplenism. Surgery was performed, and clinical remission was maintained without pancytopenia. This is the first report of a CD patient with pancytopenia caused by hypersplenism that was triggered by gastro-colic fistula-associated splenic vein obstruction.

Key words: Crohn's disease, pancytopenia, hypersplenism, gastro-colic fistula, splenomegaly

(Intern Med 62: 69-74, 2023)
(DOI: 10.2169/internalmedicine.9590-22)

Introduction

Crohn's disease (CD) is a chronic inflammatory disease of unknown etiology with periods of relapse and remission. It is a progressive disease leading to bowel damage and disability. Therefore, fistula formation represents one of the most serious complications of CD (1, 2).

Pancytopenia is a decrease in all three blood cell line counts. It is not a disease by itself but a finding due to an underlying disease process affecting the bone marrow or peripheral cells (3). Hypersplenism, which is characterized by splenomegaly, causes pancytopenia by splenic sequestration or hemolysis (4). The causes of hypersplenism are numerous, and splenectomy should be considered if appropriate. Pancytopenia is an uncommon complication of inflammatory bowel disease (IBD), with most cases developing pancytopenia from IBD treatment.

We herein report a CD patient with pancytopenia caused by hypersplenism triggered by splenic vein obstruction in association with a gastro-colic fistula.

Case Report

In April 2017, a 24-year-old Japanese woman was admitted to the Asahikawa Medical University Hospital due to abdominal pain, diarrhea, weight loss, and a high fever. She had experienced various symptoms for seven years without visiting a hospital.

A physical examination revealed the following: body height of 160.0 cm, body weight of 42.0 kg, body mass index of 16.4, body temperature of 38.1℃, blood pressure of 128/71 mmHg, heart rate of 126 beats/min, and SpO_2 of 98% on room air. A further physical examination revealed generalized abdominal tenderness, a palpable spleen, and a perianal abscess. A laboratory examination revealed high levels of inflammatory markers, remarkable anemia, and hypoalbuminemia. Specifically, the tests showed a white blood cell (WBC) count of 12,500/μL, hemoglobin of 6.2 g/dL, platelet count of 34.1×10^4/μL, C-reactive protein (CRP) of

[1]Division of Metabolism and Biosystemic Science, Gastroenterology, and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Japan and [2]Department of Diagnostic Pathology, Asahikawa Medical University Hospital, Japan
Received: February 14, 2022; Accepted: April 10, 2022; Advance Publication by J-STAGE: May 21, 2022
Correspondence to Dr. Nobuhiro Ueno, u-eno@asahikawa-med.ac.jp

Table. The Result of Laboratory Examinations.

	On admission	Prior IFX-BS initiation	Post IFX-BS initiation	Post-embolization	Post-surgery	One year after surgery
WBC, /μL	12,500	3,130	1,440	1,670	7,580	7,070
RBC, $\times10^4$/μL	401	483	430	433	342	528
Hb, g/dL	6.2	10.6	10.8	10.8	9.2	12.9
Plt, $\times10^4$/μL	34.1	15.2	8.7	12.5	73.2	32.3
Fib, mg/dL	318	-	273	190	-	237
PT-INR	1.27	-	1.13	1.13	1.15	1.03
APTT, s	37.4	-	37.2	39.3	32.7	39.6
FDP, μg/mL	2.6	-	2.5	2.7	-	2.5
TP, g/dL	6.9	7.2	7.0	7.1	6.9	7.3
ALB, g/dL	2.7	3.5	3.6	3.8	3.4	4.1
T-Bil, mg/dL	0.6	0.5	0.5	0.4	0.3	0.6
AST, U/L	9	31	23	19	17	24
ALT, U/L	6	14	17	15	7	20
CRP, mg/dL	12.16	0.30	0.10	0.10	0.10	0.10
CMV- pp65	Negative	-	Negative	-	-	-
HSV-IgM	-	-	Negative	-	-	-
HSV-IgG	-	-	Positive	-	-	-
EBV-VCA-IgM	-	-	Negative	-	-	-
EBV-VCA-IgG	-	-	Positive	-	-	-
EBNA	-	-	Positive	-	-	-
ANA	<40	-	<40	-	-	-

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Plt: platelet, Fib: fibrinogen, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin degradation products, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, CMV-pp65: cytomegalovirus-pp65 antigen, HSV: herpes simplex virus, IgM: immunoglobulin M, IgG: immunoglobulin G, EBV-VCA: Epstein-Barr virus-viral capsid antigen, EBNA: Epstein-Barr virus nuclear antigen, ANA: antinuclear antibody, IFX-BS: infliximab-biosimilar

12.16 mg/dL, and albumin of 2.7 g/dL (Table).

Upper gastrointestinal endoscopy showed wide-ranging gastric varices in the upper body and a small fistula. Colonoscopy revealed severe stenosis due to inflammatory polyps in the splenic flexure, which could not be passed, multiple longitudinal ulcer scars from the descending colon to the sigmoid colon, and a huge rectal-vaginal fistula in the lower rectum (Fig. 1). A radiographic image enhanced by amidotrizoate sodium meglumine showed a long fistula from the stomach to the descending colon, severe stenosis in the transverse colon, and a rectal-vaginal fistula in the lower rectum (Fig. 2). Contrast-enhanced computed tomography (CT) of the abdomen demonstrated huge gastric varices in the gastric wall, fistula formation from the upper stomach via the hilum of the spleen to the descending colon, which was identified by amidotrizoate sodium meglumine enhancement, splenomegaly, and multifocal inflammatory wall thickening with stenosis in the ileocecum. Furthermore, the gastric varices in the short gastric vein, narrowing of the splenic vein, and collateral circulation development were clearly demonstrated on a three-dimensional (3D) reconstructed image (Fig. 3).

A pathological examination did not identify granuloma in the longitudinal ulcer scar of the sigmoid and descending colon. She was therefore diagnosed with ileocolonic CD complicated with gastric varices, gastro-colic fistula, rectal-vaginal fistula, ileocecal stenosis, and splenomegaly based on the endoscopic findings and cross-section imaging. Her CD activity index was 213. Oral intake was not possible because of the gastro-colic fistula and severe ileocecal stenosis. Intravenous administration of broad-spectrum antibiotics and an infliximab-biosimilar (IFX-BS) 5 mg/kg without an immunomodulator as well as total parenteral nutrition were initiated as induction therapy before surgery because of the severe malnutrition and inflammation.

At 4 weeks after the initial treatment, the WBC, red blood cell (RBC), and platelet counts had markedly decreased to 1,440/μL, 385×10^4/μL, and 8.7×10^4/μL, respectively. In addition, her fever, serum albumin (3.9 g/dL), and CRP (<0.1 mg/dL) levels had improved, leading to a diagnosis of pancytopenia (Table). Serological tests for cytomegalovirus, herpes virus, and Epstein Barr virus infection were all negative. No serum autoantibodies, including anti-nuclear antibodies, were detectable (Table). A bone marrow aspiration (BMA) examination showed normoplastic bone marrow without malignant cells. Her pancytopenia was thus considered to be caused by hypersplenism triggered by splenic vein obstruction in association with the gastric-colic fistula shown on endoscopy and CT.

Splenic artery embolization was performed, although her pancytopenia did not improve due to the rich collateral circulation. The laboratory tests showed a WBC count of

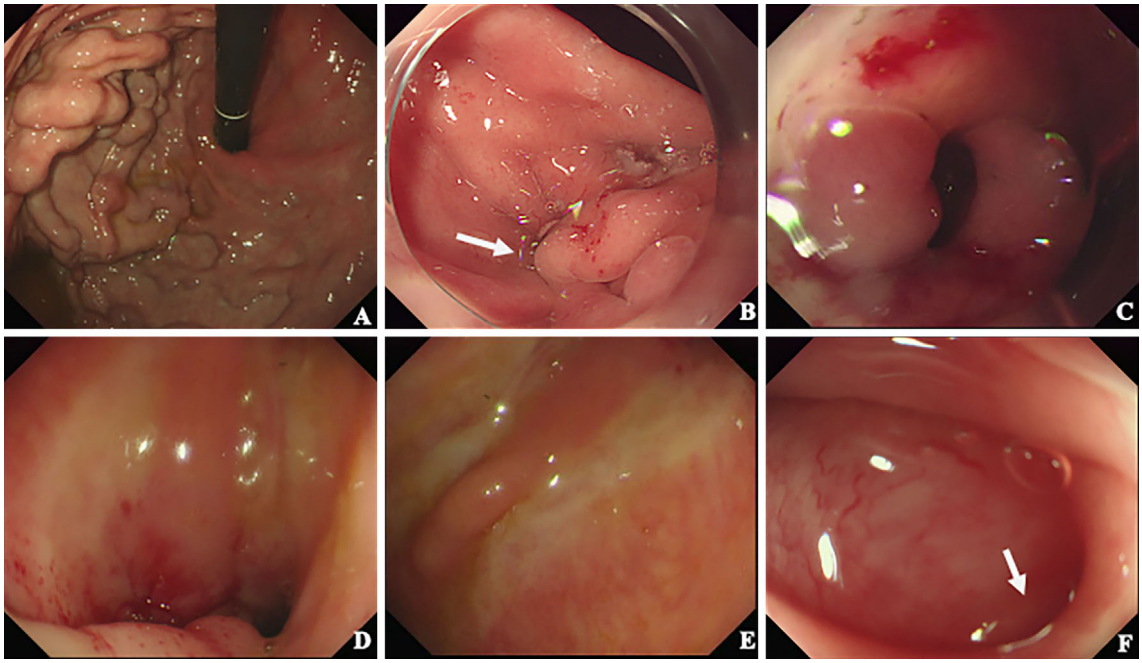

Figure 1. **A: Wide-ranging gastric varices in the upper body. B: A small fistula within the gastric varices (white arrow). C: A gastric fistula. D: Severe stenosis in the splenic flexure of the colon. E: Multiple longitudinal ulcer scars from the descending colon to the sigmoid colon. F: A rectal-vaginal fistula (white arrow). A-C: Upper gastrointestinal endoscopy. D-F: Colonoscopy.**

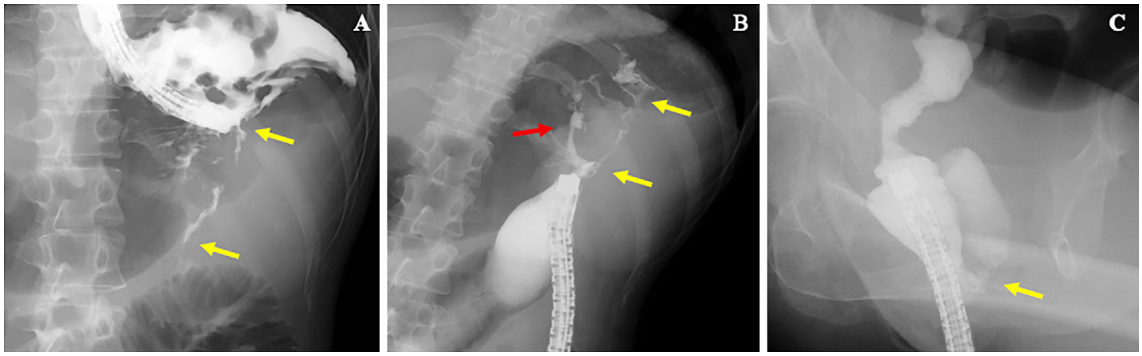

Figure 2. **A: A long fistula from the stomach to the descending colon (yellow arrows). B: A long fistula from the descending colon to the stomach (yellow arrows) and severe stenosis in the transverse colon (red arrow). C: A rectal-vaginal fistula in the lower rectum (yellow arrow). A-C: A radiographic image enhanced by amidotrizoate sodium meglumine.**

1,670/μL, RBC count of 433×10^4/μL, hemoglobin level of 10.8 g/dL, and platelet count of 12.5×10^4/μL (Table). Therefore, surgical treatment, with resection of the terminal ileum and total colon, splenectomy, partial gastrectomy, and ileostomy was performed in September 2017. The pathological findings after surgery demonstrated multiple nonspecific ulcer scars in the terminal ileum and throughout the colon, multiple inflammatory polyps with a fistula in the splenic flexure of the colon, an abscess with a fistula in the stomach, and multiple stenoses and thrombi in the splenic vein in the splenectomy specimen (Fig. 4). Her pancytopenia improved immediately after the surgery, as a laboratory examination revealed a WBC count of 7,580/dL, RBC count of 342×10^4/μL, hemoglobin level of 9.2 g/dL, and platelet count of 73.2×10^4/dL (Table). Oral intake was initiated, and she was discharged in November 2017.

In September 2018, a year after the surgery, upper gastrointestinal endoscopy revealed a sliding hernia formed by the deformed stomach and the surgical scar from partial gastrectomy without gastric varices in the upper body. A radiographic image enhanced by amidotrizoate sodium meglumine did not detect any fistula in the stomach. Furthermore, the huge gastric varices in the gastric wall had completely disappeared on enhanced CT of the abdomen (Fig. 5). A laboratory examination revealed the following: WBC count of 7,070/dL, RBC count of 528×10^4/μL, hemoglobin level of 12.9 g/dL, and platelet count of 32.3×10^4/dL (Table). Clinical remission was thus maintained by IFX-BS therapy without pancytopenia.

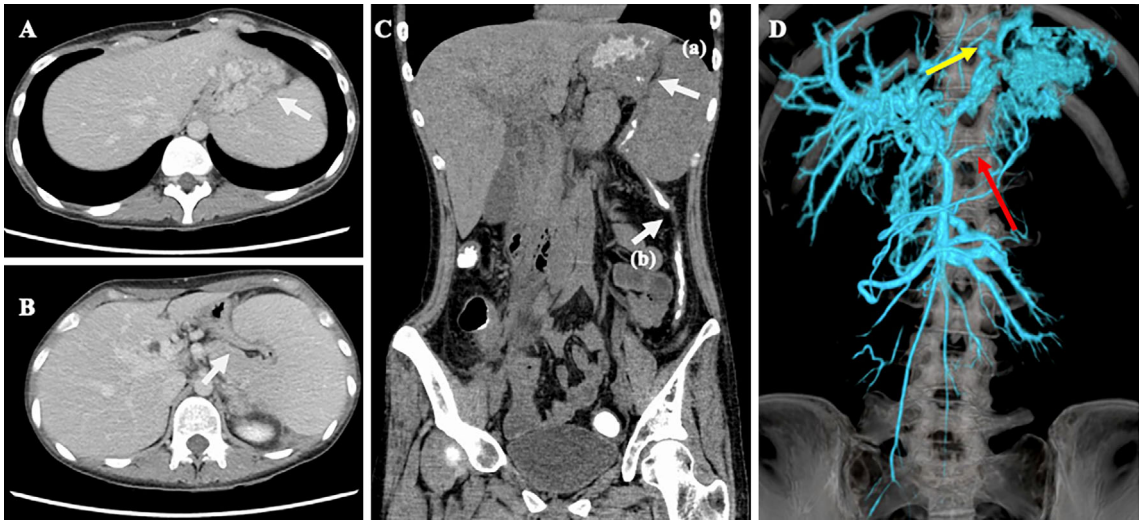

Figure 3. **A: Gastric varices in the gastric wall (white arrow). B: Fistula formation from the upper stomach to the hilum of the spleen with splenomegaly (white arrow). C: The long fistula from the stomach [white arrow (A)] to the descending colon [white arrow (B)]. D: Gastric varices formation in the short gastric vein (yellow arrow), narrowing of the splenic vein (green arrow), and collateral circulation development. A: A contrast-enhanced image. B: An amidotrizoate sodium meglumine-enhanced image. C: A three-dimensionally reconstructed image.**

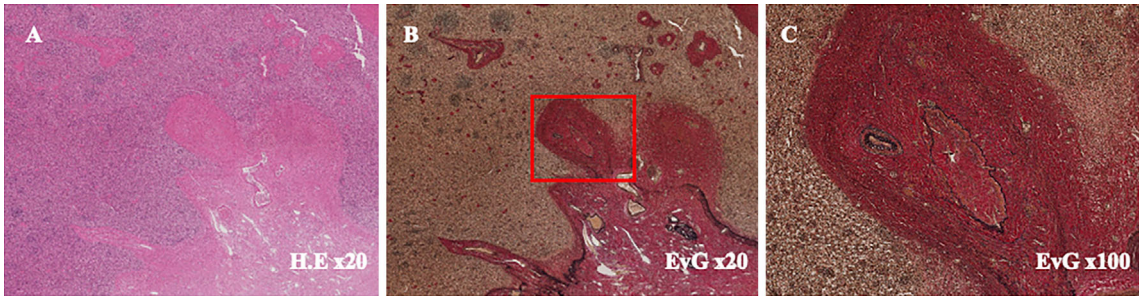

Figure 4. **A Thrombus in the splenic vein in the splenectomy specimen. A: 20-fold magnification of Hematoxylin and Eosin staining (H&E), B: 20-fold magnification of Elastica van Gieson (EvG) staining. C: 100-fold magnification of EvG staining.**

Discussion

To our knowledge, this is the first report to describe a CD patient with pancytopenia caused by hypersplenism triggered by splenic vein obstruction in association with gastric-colic fistula. Pancytopenia in CD patients has been reportedly induced by various factors, including viral infection (5, 6), immunomodulators (7, 8), autoimmune disease (9), and hematological malignancy, such as lymphoproliferative disorders (10). In this study, none of these factors were present, and splenectomy was dramatically effective. These two points indicate that the pancytopenia was caused by gastro-colonic fistula-associated hypersplenism in this CD patient. Physicians should pay be alert for secondary hypersplenism associated with intestinal inflammation and fistula when pancytopenia is detected in CD patients without any infections, malignancies, or bone marrow-suppressive drugs.

In the present case, the pancytopenia did not appear on admission. All blood cell line counts progressively decreased after the inflammation was relieved by IFX-BS treatment. We hypothesized that chronic inflammation with severe complications might have increased the WBC and platelet counts. The adverse effects of the drugs were initially suspected to be the cause when the pancytopenia became apparent. However, azathioprine, a bone marrow-suppressant, was not used in the present case. In addition, a BMA examination showed a normoplastic marrow without malignant cells, indicating a low likelihood of drug-induced bone marrow suppression. Serological tests for cytomegalovirus, herpes virus, and Epstein Barr virus infection were all negative, and no serum autoantibodies were detected, indicating that pancytopenia had not been caused by infection or autoimmune disease. CT showed splenomegaly, narrowing of the splenic vein with collateral circulation development, and gastric varices. Therefore, we concluded that the pancytopenia in this case had been caused by gastro-colic fistula-associated hypersplenism, based on the diagnostic proce-

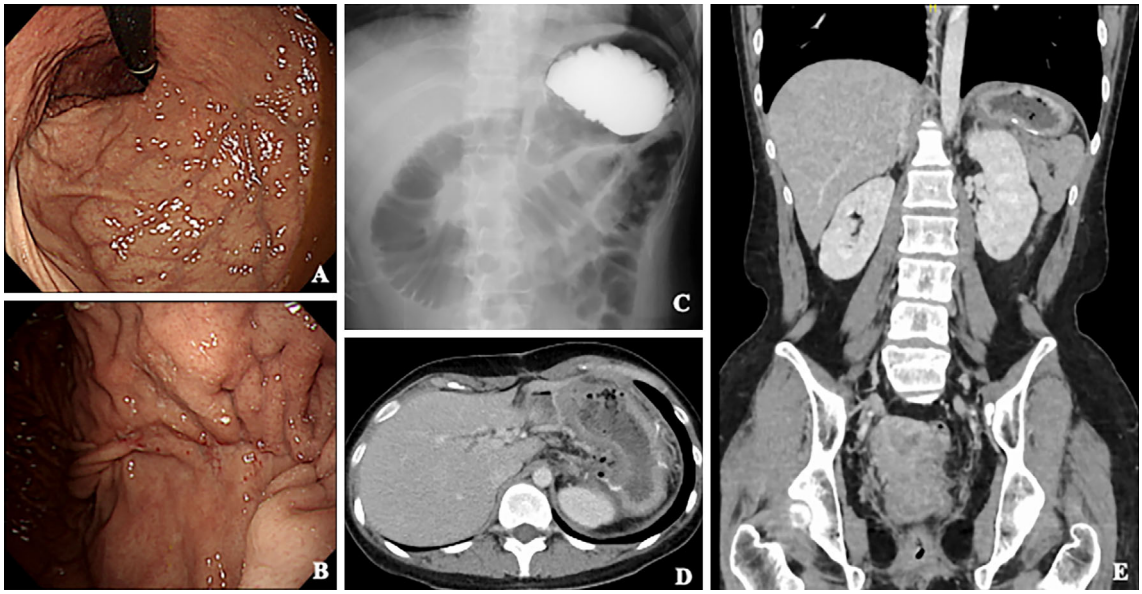

Figure 5. **A: Sliding hernia and disappearance of the gastric varices. B: Surgical scar from partial gastrectomy in the upper body. C: Disappearance of the fistula from the stomach. D: Disappearance of gastric varices in the gastric wall. E: Post-splenectomy. A-B: Upper gastrointestinal endoscopy. C: A radiographic image enhanced by amidotrizoate sodium meglumine. D-E: A contrast-enhanced image.**

dures.

In the postoperative specimen, multiple inflammatory polyps with a fistula in the splenic flexure of the colon, an abscess with a fistula in the stomach, and multiple sites of narrowing and thrombi in the splenic vein were detected. Ando et al. reported that venous thrombosis was more frequently found in IBD patients than in those with other digestive diseases (11). In the present case, severe inflammation in the splenic flexure of the colon might have led to microperforation and abscess formation in the hilum of the spleen. In addition, the microabscess might have caused severe inflammation and perforation of the upper stomach. We suspect that the long gastro-colic fistula might have developed via these mechanisms. Chronic inflammation from gastro-colic fistula with the abscess was thought to have to led to the narrowing and thrombosis of the splenic vein thereafter, interfering with anomalous splenic venous return and leading to the development of splenomegaly and gastric varices. Consequently, we suspect that gastro-colic fistula affected the portal vein system and led to severe pancytopenia. Physicians should be aware that severe chronic inflammation with a fistula can affect the portal system, leading to hypersplenism in CD patients.

According to the Vienna classification, three subgroups of patients were identified based on the disease behavior: B1, purely inflammatory (nonstricturing nonpenetrating); B2, fibrostenotic; and B3, penetrating (12). Most CD patients actually have a nonpenetrating nonstricturing phenotype at the diagnosis, although this phenotype progresses to stricturing disease with penetrating lesions over the long term (13, 14). Thus, the natural history of CD leads to irreversible bowel damage and disability in most CD patients. In the present case, seven years had passed since the onset of CD. Consequently, severe complications, including multiple and complex fistulas, had formed. In a randomized trial comparing early intensive treatment with combined immunosuppression (top-down) and conventional step-up treatment in CD patients, the former showed an improved cumulative nonrelapse rate, demonstrating the benefit of reducing the accumulation of intestinal damage in newly diagnosed patients (15). Even in the present case, early intensive treatment including biologics might have helped the patient avoid massive intestinal resection and prevent serious complications, including pancytopenia.

In conclusion, this is the first report of a CD patient with pancytopenia caused by hypersplenism that was triggered by gastro-colic fistula-associated splenic vein obstruction. CT with amidotrizoate sodium meglumine and serological examinations confirmed fistula-associated splenic vein obstruction and ruled out such complications as infections and other autoimmune diseases. Physicians should be alert for secondary hypersplenism associated with intestinal inflammation and fistula when pancytopenia is detected in CD patients. The combination of pharmacological therapy and surgery was able to improve both the intestinal inflammation and pancytopenia based on a correct diagnosis. CD is a progressive disease leading to irreversible bowel disability; therefore, this case report emphasizes the importance of correctly assessing the disease state in CD patients by performing appropriate examinations and diagnostic imaging.

Author's disclosure of potential Conflicts of Interest (COI).
Mikihiro Fujiya: Honoraria, AYUMI Pharmaceutical Corporation, Mitsubishi Tanabe Pharma Corporation, Nippon Kayaku and

Pfizer.

References

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet **389**: 1741-1755, 2017.
2. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis **17**: 1415-1422, 2011.
3. Gnanaraj J, Parnes A, Francis CW, Go RS, Takemoto CM, Hashmi SK. Approach to pancytopenia: diagnostic algorithm for clinical hematologists. Blood Rev **32**: 361-367, 2018.
4. Jandl JH, Aster RH, Forkner CE, Fisher AM, Vilter RW. Splenic pooling and the pathophysiology of hypersplenism. Trans Am Clin Climatol Assoc **78**: 9-27, 1967.
5. Haag LM, Hofmann J, Kredel LI, et al. Herpes simplex virus sepsis in a young woman with Crohn's disease. J Crohns Colitis **9**: 1169-1173, 2015.
6. Pop CS, Becheanu G, Calagiu D, et al. A rare complication of CMV infection in Crohn's disease - hemophagocytic syndrome: a case report. Rom J Morphol Embryol **56**: 1535-1540, 2015.
7. Choi YS, Suh JP, Song KH, et al. A case of Crohn's disease with improvement after azathioprine-induced pancytopenia. Case Rep Gastroenterol **5**: 344-349, 2011.
8. Kakuta Y, Naito T, Onodera M, et al. NUDT15 R139C causes thiopurine-induced early severe hair loss and leukopenia in Japanese patients with IBD. Pharmacogenomics J **16**: 280-285, 2016.
9. Uzzan M, Galicier L, Gornet JM, et al. Autoimmune cytopenias associated with inflammatory bowel diseases: insights from a multicenter retrospective cohort. Dig Liver Dis **49**: 397-404, 2017.
10. Jansson-Knodell CL, Walker MJ, Fischer M. Pancytopenia in a young male patient with inflammatory bowel disease. Gastroenterology **168**: 1483-1485, 2020.
11. Ando K, Fujiya M, Nomura Y, et al. The incidence and risk factors of venous thromboembolism in patients with inflammatory bowel disease: a prospective multicenter cohort study. Digestion **100**: 229-237, 2019.
12. Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis **6**: 8-15, 2000.
13. Louis E, Collard A, Oger AF, et al. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. Gut **49**: 777-782, 2001.
14. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis **8**: 244-250, 2002.
15. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet **371**: 660-667, 2008.