—Case Reports—

Ravulizumab Can Effectively Treat Ischemic Enteritis Caused by Paroxysmal Nocturnal Hemoglobinuria

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Ischemic colitis is a common disease with a good prognosis; however, complications can occur in the presence of a serious underlying disease. Herein, we present a case report in which characteristic findings on lower gastrointestinal endoscopy led to a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH). An 82-year-old woman visited our hospital for chronic heart and renal failure. She had a history of breast cancer, myocardial infarction, and hemorrhoidal fistula and was initially hospitalized for ischemic colitis. Subsequent lower gastrointestinal endoscopy revealed extensive ulcerative lesions in the ascending, transverse, and descending colon. Histopathologically, small vessels exhibited multiple fibrin thrombus formations. Based on histopathological and endoscopic results, the presence of an underlying disease was suspected. Flow cytometric analysis showed that erythrocytes and granulocytes had 5.5 and 86.4% CD55- and CD59-negative cells, respectively. The patient was ultimately diagnosed with PNH and considered severely ill, given the ischemic colitis-induced abdominal pain and the need for red blood cell transfusions (4-6 units per month). Accordingly, the patient was administered ravulizumab. Ischemic enteritis did not relapse following ravulizumab administration, and transfusion dependence improved. If a patient with ischemic colitis presents atypical lower gastrointestinal endoscopic findings, it is important to explore the presence of an underlying disease.
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Key words: ravulizumab, paroxysmal nocturnal hemoglobinuria, ischemic enteritis, hemolytic anemia, lower gastrointestinal endoscope

Introduction

Ischemic colitis is a common disease caused by temporary ischemia of the arteries connected to the large intestine, and patients frequently complain of abdominal pain and bloody stools. Arteriosclerosis and aging are common underlying causes. Hemodialysis, hypertension, hypoalbuminemia, diabetes mellitus, and constipation have been identified as risk factors[1–3]. The presence of underlying disease should be carefully considered, given that extremely rare reports of ischemic colitis caused by sickle cell disease or systemic lupus erythematosus have been documented[1,4,5].

Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disease characterized by complement-induced intravascular hemolysis resulting from clonal expansion of hemopoietic stem cells with acquired mutations in the *PIGA* gene, which may be complicated by thrombosis[6]. Although the pathogenesis of thrombosis remains unclear, possible underlying mechanisms include platelet activation, effects of intravascular hemolysis, and complement attack on glycosyl phosphatidylinositol anchor deficient cells[7,8]. Schrezenmeier et al.[9] analyzed 1,610 patients with PNH and found that 15.5% had a history of thrombosis at enrollment. Hillmen et al.[10]

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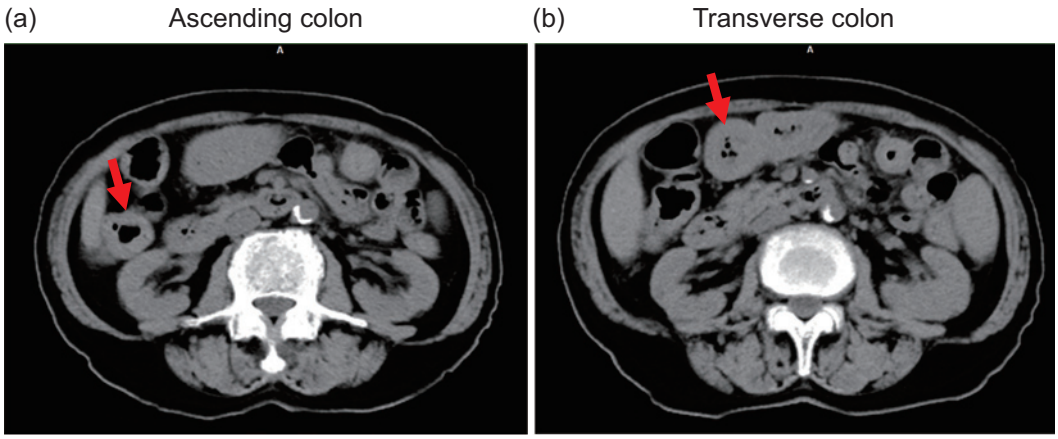

Fig. 1 Computed tomography in the 82-year-old patient
(a) Thickening of the intestinal wall of the ascending colon (red arrow)
(b) Thickening of the intestinal wall of the transverse colon (red arrow)

examined the site of thrombosis in 124 patients with PNH, reporting that deep vein thrombosis was the most common site (33.1%), whereas 18.5% of patients exhibited enterocolic and splenic vein thrombosis. Although PNH is a rare disease with a reported incidence of 15.9 per million in Europe and the United States, it should be considered in the presence of thrombosis[11].

Herein, we present a case in which a patient was hospitalized with a diagnosis of ischemic colitis; however, characteristic findings on lower gastrointestinal endoscopy ultimately led to a diagnosis of PNH.

Case Report

An 82-year-old woman visited our hospital for renal failure and chronic heart failure due to the myocardial infarction that occurred 1 year ago. She also had a history of breast cancer and hemorrhoidal fistula and was under treatment with azosemide 60 mg/day, rosuvastatin 2.5 mg/day, linagliptin 5 mg/day, clopidogrel 75 mg/day, rabeprazole 10 mg/day, carvedilol 1.25 mg/day, sennoside 0.5 g/day, ramelteon 8 mg/day, eszopiclone 2 mg/day, and suvorexant 15 mg/day. She visited the outpatient department of internal medicine with a chief complaint of abdominal pain that began at 3:00 a.m. Computerized tomography revealed extensive edematous changes from the transverse colon to the descending colon, and ischemic colitis or bacterial enteritis was suspected (**Fig. 1**). The previous physician recommended bowel rest and prescribed levofloxacin 500 mg. However, two nights later, the patient visited the emergency room because of worsening abdominal pain. A blood test revealed hemoglobin of 7.8 g/dL, high lactate dehydrogenase value (874 U/L), and an increased reticulocyte count (64,800/μL). Urine occult blood was 1+ and urine urobilinogen was normal. The patient had no signs of jaundice and she was admitted with the objective of bowel rest with a diagnosis of hemorrhagic anemia due to exacerbation of ischemic colitis.

After admission, the patient fasted and received supplemental fluids, and her abdominal pain gradually decreased. On day 6, upper and lower gastrointestinal endoscopy revealed extensive ulcerative lesions in the ascending, transverse, and descending colon (**Fig. 2**). Histopathological examination revealed multiple fibrin thrombus formations in the small vessels, suggesting microangiitis (**Fig. 3**).

Based on the histopathological and endoscopic results, we suspected the presence of an underlying hematological disease. A bone marrow aspiration revealed normal chromosomes and no atypical suspicions of myelodysplastic syndrome. Haptoglobin level was below sensitivity, and lactate dehydrogenase was elevated, suggesting hemolytic anemia. The Coombs test was negative. Flow cytometry examined peripheral blood lymphocyte surface antigen expression, demonstrating 5.5% CD55- and CD59-negative cells in erythrocytes and 86.4% in granulocytes (**Table 1**). Based on these results, a diagnosis of PNH was established. The patient was discharged from the hospital on day 21.

After hospital discharge, the patient experienced bloody stools and abdominal pain on day 53, which resolved spontaneously. The patient was considered severely ill, given the abdominal pain symptoms attributed to ischemic colitis and the need for red blood cell transfusions (4-6 units per month). Following meningitis vaccination (Menactra vaccine), 2,400 mg of ravulizumab

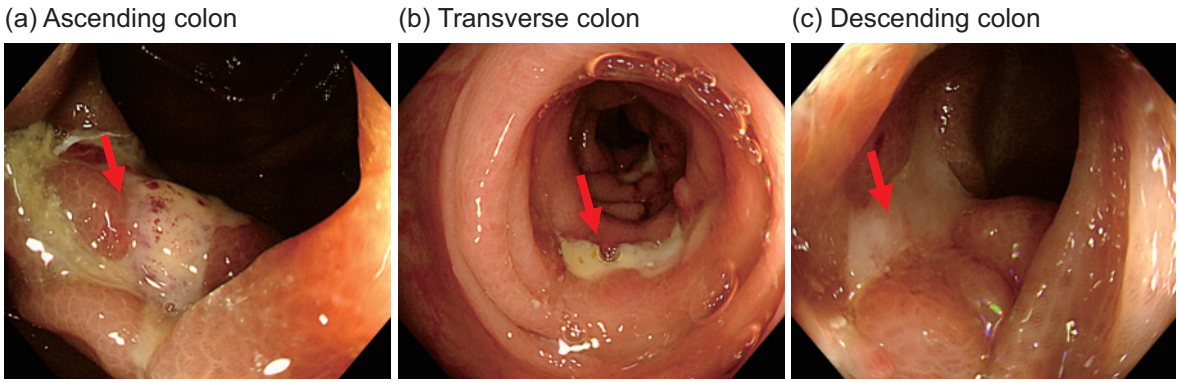

Fig. 2 Lower gastrointestinal endoscopy in the 82-year-old patient
(a) Ulcers at the ascending colon (red arrow)
(b) Ulcers at the transverse colon (red arrow)
(c) Ulcers at the descending colon (red arrow)

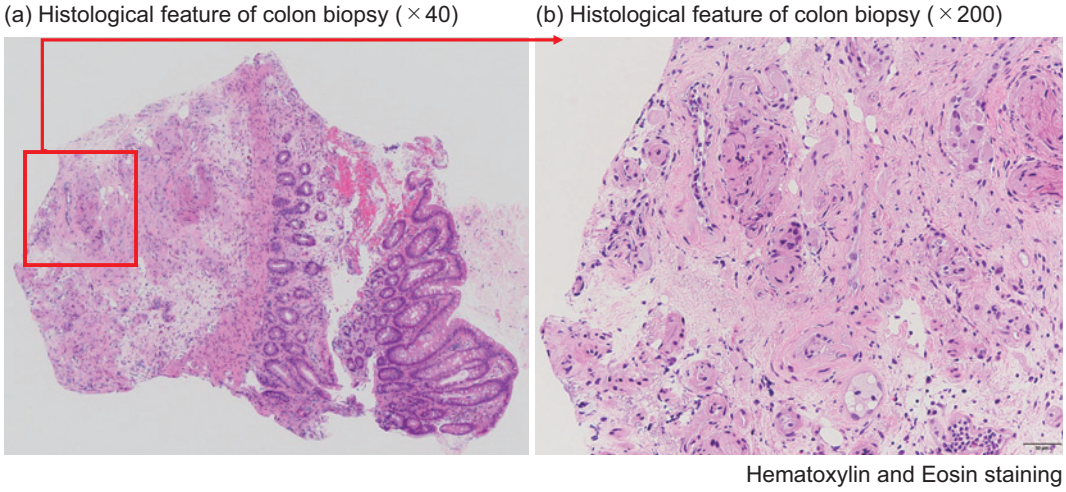

Fig. 3 Histologic features of colon biopsy (Hematoxylin and Eosin staining, 40× (a) and 200× (b))
(a) Erosion with a reduced number of crypts and edema in the lamina propria, along with the proliferation of dilated capillaries in the submucosa.
(b) Magnification of the image within the framed rectangle. Fibrin thrombus in capillaries within the submucosal layer was observed.

was administered on day 62, followed by 3,000 mg of ravulizumab on day 76. As we had no experience in administering ravulizumab at Fussa Hospital, we referred the patient to the university hospital for initial treatment, which delayed the start of treatment. Thereafter, ravulizumab 3,000 mg was administered every 56 days at Fussa Hospital. Given the presence of chronic kidney disease, darbepoetin alfa and epoetin beta pegol were also administered. No relapse of ischemic colitis occurred, and the frequency of blood transfusions improved to approximately 2 units every 1-2 months (**Fig. 4**). The patient developed a urinary tract infection on day 158, which improved following treatment with ceftriaxone.

Informed consent was obtained from the patient in accordance with the Declaration of Helsinki, and the Institutional Review Board of Fussa Hospital approved this study (approval number: 2021-43).

Discussion

Thrombosis is a common complication in patients with PNH, and 15.4% of patients had history of thrombosis at diagnosis especially when PNH blood cells in granulocytes exceed 50%[9]. Sixteen cases of ischemic enteritis associated with PNH have been reported, with seven cases warranting surgical intervention, which can be a fatal complication[12]. In the present case, CD55-negative and CD59-negative cells in granulocytes were as high as 86.4%, and the patient was older and also had diabetes mellitus, and exhibited a markedly high risk of thrombosis. She had a history of myocardial infarction, which

Table 1 Laboratory findings

WBC	5,600 /μL	TP	5.5 g/dL	COVID-19 PCR	negative
(Neut 69.2%, Lympo 24.5%, Mono 5.7%, Eosino 0.2%, Baso 0.4%)		Alb	3.6 g/dL		
		BUN	27.1 mg/dL	Fecal occult blood test	positive
RBC	2.3×10^6 /μL	Creat	2.3 mg/dL		
Hb	7.8 g/dL	T-bil	1.19 mg/dL	Urinary test (occult blood)	1+
Hct	22.8 %	AST	29 U/L	Urinary test (urobilinogen)	normal
MCV	99.6 fL	ALT	9 U/L		
MCH	34.1 pg	LDH	874 U/L		
MCHC	34.2 g/dL	(LDH1 37.1%, LDH2 40.6%, LDH3 14.5%,			
Plt	20.2×10^4 /μL	LDH4 4.2%, LDH5 3.6%)			
APTT	34.3 sec				
PT-INR	1.06	ALP	480 U/L		
D-dimer	5.7 μg/mL	γ-GTP	20 U/L		
CD55- CD59- negative cells in erythrocytes	5.5 %	Na	136.9 mEq/L		
CD55- CD59- negative cells in granulocytes	86.4 %	K	3.4 mEq/L		
		Cl	97 mEq/L		
		CRP	11.2 mg/dL		
		BS	121 mg/dL		
		Erythropoietin	51.4 mIU/L		
		Haptoglobin	10>		
		Anti nuclear antibody	negative		
		Direct-coobs test	negative		
		Indirect-coobs test	negative		

Abbreviations: Alb, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BS, blood sugar; BUN, blood urea nitrogen; CD, clusters of differentation; COVID-19, coronavirus disease 2019; Creat, creatinine; CRP, C-reactive protein; γ-GTP, γ-glutamyl transpeptidase; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Plt, platelet; PT-INR, prothrombin time-international normalized ratio; RBC, red blood cell; T-bil, total bilirubin; TP, total protein; WBC, white blood cell.

may have been affected by PNH.

Ischemic colitis occurs in the descending and sigmoid colon, located farthest from the superior and inferior mesenteric arteries and most susceptible to ischemia, with patients often experiencing left-sided abdominal pain. Conversely, right-sided abdominal pain can be attributed to an underlying disease, which is reportedly more severe[1,3]. Montoro et al.[3] analyzed 364 patients with ischemic colitis and reported that 58.0% had ischemia in the descending colon and 69.5% in the sigmoid colon.

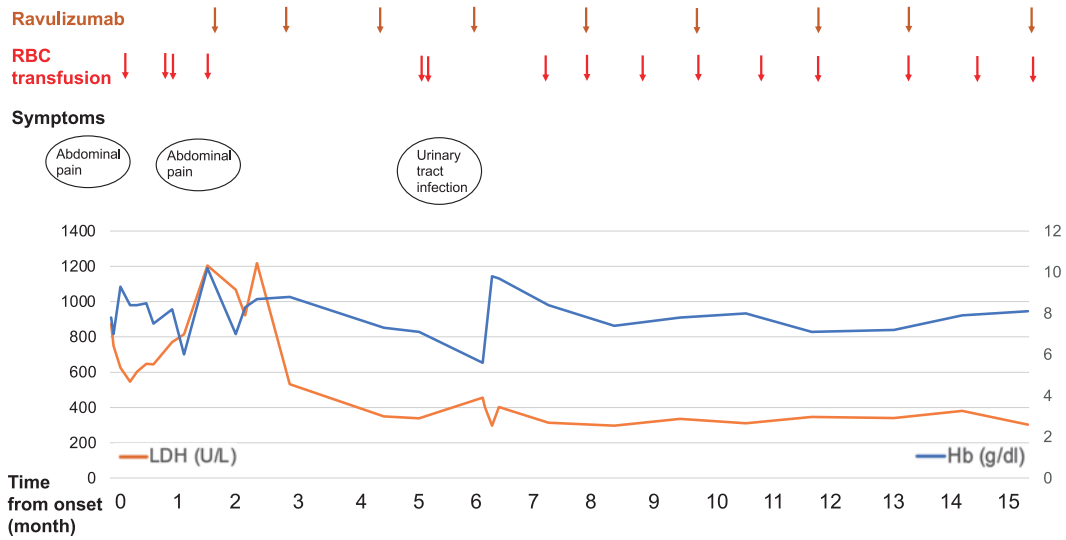

Fig. 4 Clinical time course of the 82-year-old patient with paroxysmal nocturnal hemoglobinuria
Abbreviations: Hb, hemoglobin; LDH, lactate dehydrogenase; RBC, red blood cell

Moreover, the authors found that patients with ischemic findings in the right intestinal tract had a poor prognosis[3]. Multiple ulcers occurred from the ascending colon to the sigmoid colon in cases with systemic lupus erythematosus, and multiple lesions in the intestinal tract were a feature of PNH-induced ischemic enteritis[5,13]. In the present case, ulcers were extensively present in the ascending, transverse, and descending colon on lower gastrointestinal endoscopy, which led us to suspect that ischemic colitis could be attributed to an underlying disease.

Thrombosis is reportedly the primary cause of death in patients with PNH, although treatment with eculizumab substantially reduced thrombosis and markedly improved the prognosis of PNH[6,10]. Ravulizumab, a drug with an extended half-life compared to that of eculizumab, has been shown not to be inferior to eculizumab and is now widely used[14]. Eculizumab and ravulizumab have greatly improved the prognosis of PNH; however, challenges need to be addressed. First, approximately 20% of patients also require blood transfusions after receiving eculizumab or ravulizumab, most likely due to extravascular hemolysis[1]. Next, eculizumab and ravulizumab inhibit the complement pathway, and caution should be exercised in severe infections caused by capsid-forming bacteria[1]. The present patient did not experience a recurrence of ischemic colitis after ravulizumab administration, and urinary tract infection rapidly improved with antimicrobial therapy. Transfusion dependence persisted, and extravascular hemolysis was considered a possible effect.

Herein, we encountered a case in which PNH was suspected based on characteristic lower gastrointestinal endoscopic findings in a patient hospitalized for ischemic colitis, and the early introduction of ravulizumab afforded favorable outcomes. When a patient with ischemic colitis presents atypical lower gastrointestinal endoscopic findings, it is important to explore the presence of an underlying disease.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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