□ CASE REPORT □

Autoimmune Hemolytic Anemia Triggered by Infection with Human Parvovirus B19 after Total Abdominal Colectomy for Ulcerative Colitis

Tomoya Iida¹, Shuji Satoh¹, Suguru Nakagaki², Haruo Shimizu¹ and Hiroyuki Kaneto¹

Abstract

A 50-year-old man was admitted to our hospital for an adhesive ileus 14 years after total abdominal colectomy for ulcerative colitis (UC). The ileus decreased with conservative treatment, however, autoimmune hemolytic anemia (AIHA) was diagnosed due to worsening anemia, a positive direct Coombs test, low haptoglobin, high lactate dehydrogenase, reticulocytosis, and an increase in the erythroblastic series in a bone-marrow examination. Human parvovirus B19 (PV-B19) IgM and PV-B19 DNA were present, indicating the development of AIHA triggered by an infection with PV-B19. The patient is currently being monitored after spontaneous remission. This is the first report of UC after total abdominal colectomy complicated by AIHA triggered by PV-B19 infection.

Key words: ulcerative colitis, autoimmune hemolytic anemia, human parvovirus B19, total abdominal colectomy

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that is of unknown cause, but may involve an autoimmune mechanism, based on the association of UC with other autoimmune diseases. UC complicated by autoimmune hemolytic anemia (AIHA) has been previously described, mainly in Western countries, however, UC with AIHA after total abdominal colectomy has not yet been reported. In this case, infection with human parvovirus B19 (PV-B19) was involved in the onset of AIHA. We herein report this case with an accompanying literature review.

Case Report

The patient was a 50-year-old man with a major complaint of jaundice. He had a history of right inguinal hernia. His family history was unremarkable. The patient was admitted to our hospital for treatment of pancolitis-type severe

UC in September 1999. He was unresponsive to high-dose intravenous (IV) prednisolone and protracted IV cyclosporine. Emergency total abdominal colectomy and ileostomy were performed, followed by two-stage proctectomy and ileal J-pouch anal anastomosis in 2000. Subsequently, the condition of the patient did not show any significant changes.

In June 2014, the patient visited our hospital due to abdominal pain. He was diagnosed with postoperative adhesive ileus after a close examination and was hospitalized. The ileus became less severe with conservative treatment, and the patient was discharged on hospital day 8. However, he had a major complaint of jaundice 5 days after discharge, and he was initially examined as an outpatient and then re-hospitalized.

At admission, the patient had a normal appearance and a body temperature of 37.3°C. He felt alert and had no neurological abnormalities. There was no sign of anemia in the palpebral conjunctiva, however, yellowing of the bulbar conjunctiva was apparent. Yellowing of the entire skin was also

¹Department of Gastroenterology, Muroran City General Hospital, Japan and ²Department of Gastroenterology, Otaru City General Hospital, Japan

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Correspondence to Dr. Tomoya Iida, tomoya.iida.0306@gmail.com

Table. Laboratory Findings at the Most Recent Admission.

Peripheral Blood		Biochemistry		Serology	
WBC	3,540 / μ L	TP	7.2 g/dL	CRP	0.3 mg/dL
Neu	2,210 / μ L	Alb	4.4 g/dL	ESR	23 mm
Lym	960 / μ L	T-Bil	9.8 mg/dL	IgG	1,020 mg/dL
Mono	330 / μ L	I-Bil	9.5 mg/dL	C3	135 mg/dL
Eos	40 / μ L	AST	27 IU/L	C4	35 mg/dL
RBC	3.37×10^6 / μ L	ALT	23 IU/L	CH50	46.5 U/mL
Hb	11.4 g/dL	LDH	810 IU/L	ANA	<40 ×
Hct	31.1 %	ALP	249 IU/L	Vit.B12	269 pg/mL
MCV	92.3 fL	γ -GTP	47 IU/L	folic acid	8.1 ng/mL
MCHC	33.8 g/dL	Cre	0.65 mg/dL	HIV Ab	(-)
Plt	218×10^3 / μ L	BUN	13.1 mg/dL	HTLV-1 Ab	(-)
Urinalysis		UA	5.5 mg/dL	EBV VCA IgG	320 ×
Occult blood	(3+)	T-chol	132 mg/dL	EBV VCA IgM	10 ×
Sugar	(-)	TG	109 mg/dL	EBV EBNA	10 ×
		Na	137 mEq/L	PV B19 IgM	(+)
		K	3.8 mEq/L	PV B19 IgG	(-)
		Cl	102 mEq/L	PV B19 DNA	(+)
		Ca	9.1 mg/dL	Haptoglobin	1 mg/dL
		Fe	106 μ g/dL	Cold agglutinin	128 ×
		Fer	877 ng/mL	Direct Coombs	(3+)
		Coagulation		Indirect Coombs	(2+)
		PT%	92 %	NAP score	220
		PT-INR	1.05	CD55CD59(-) RBC	0 %
		APTT	38.1 sec	RBC membrane	
		Fib	466 mg/dL	resistance test min.	0.43 %
		FDP	4.8 μ g/mL	RBC membrane	
		D-dimer	0.5 μ g/mL	resistance test max.	0.33 %

apparent, but with no sign of exanthema. No palpable superficial nodes were found, and there were no abnormalities in the chest and heart sounds or in the abdomen. There were also no signs of joint pain.

At the initial admission, blood tests showed a high white blood cell count, but no worsening of anemia and no increase in lactate dehydrogenase (LDH). At the most recent admission, laboratory findings (Table) showed mild normocytic normochromic anemia; a significant decrease in haptoglobin; increased T-Bil, indirect bilirubin (I-Bil), and LDH; and an increase in the reticulocyte count. A direct Coombs test (DCT) gave a score of 3⁺ and anti-human IgG antibody was positive, but anti-human IgG3b and IgG3d antibodies were both negative. There was no abnormality in cold agglutination. The percentage of CD55/CD59-negative red blood cells was 0%, and the neutrophil alkaline phosphatase score was normal. A microscopic test did not show any spherocytes, and the membrane resistance of the red blood cells was normal. PV-B19 IgM and PV-B19 DNA were both positive.

Contrast-enhanced CT of the abdomen and pelvis revealed no cause for jaundice and no findings of ileus. Lower gastrointestinal tract endoscopy indicated neither residual large intestinal mucosa nor appreciable abnormalities. In a bone-

marrow examination, the myeloid-erythroid ratio was 1.0. There was an increase in the number of erythroblasts, however, cellular atypia was unclear. There were no abnormalities in flow cytometry or in the 46 and X and Y chromosomes.

During hospitalization, AIHA was first considered according to the results of the blood tests and bone-marrow examination, however, warm-type AIHA was later diagnosed based on the absence of cold agglutinin disease and paroxysmal nocturnal hemoglobinuria. AIHA may have developed due to an initial infection of PV-B19 because both PV-B19 IgM and PV-B19 DNA were positive. Steroid therapy was planned as early treatment, however, after hospital day 2 the levels of bilirubin and LDH tended to decrease spontaneously, and there was no sign of anemia progression; therefore, a decision was made to monitor the patient after obtaining his permission. The patient was discharged on hospital day 10. At 30 days after the onset of AIHA, the levels of haptoglobin, T-Bil, I-Bil, LDH, and reticulocytes had normalized, and the DCT score was +1 (Figure). At 10 months after the onset of AIHA, the patient is recurrence-free without therapy.

Figure. Clinical course after hospitalization; Steroid therapy was planned as early treatment, but after hospital day 2 the levels of bilirubin and LDH tended to decrease spontaneously, and there was no sign of progression of anemia; therefore, a decision was made to monitor the patient, after obtaining his permission. The patient was discharged on hospital day 10. At 30 days after onset of AIHA, the levels of haptoglobin, T-Bil, I-Bil, LDH, and reticulocytes had normalized, and the DCT score was +1.

Discussion

UC is known to be associated with other autoimmune diseases (1). Lorber et al. first described UC associated with AIHA in 1955 (2), and such cases occur at a rate of 0.2 to 1.7% among all UC cases (3, 4). Most reports have been in Western countries, and AIHA is clearly a rare complication of UC. Non-drug- and drug-induced mechanisms have been proposed for AIHA. The most widely held theory for non-drug inducibility involves an increase in antigens in the pathological digestive tract lining due to UC, and the subsequent formation of erythrocytes and cross-reactive antibodies that may cause hemolysis (5, 6).

Clements et al. found that patients with UC associated with AIHA attained remission with colectomy (7), and Jacob et al. found that such patients became DCT-negative (8). These findings appear to indicate that the large intestinal mucosa has a crucial role in autoantibody production against erythrocytes. However, cases similar to our case, in which a UC patient who underwent total abdominal colectomy experienced a complication of AIHA, have also been reported (9, 10), and thus there are still many questions remaining regarding the etiological mechanisms. Sulfasalazine is an important cause of drug-induced hemolytic anemia, and Valery et al. suggested this adverse event may be in-

involved in hemolytic anemia (11). However, the patient in our case did not take sulfasalazine. There was no change in his oral medication and no use of a new drug before or after the development of hemolytic anemia; therefore, it is unlikely that hemolytic anemia was caused by sulfasalazine or other drugs in our case.

A PubMed database search indicated that there have been reports of 66 cases (27 males, 38 females, 1 unknown) with UC and associated AIHA, in which the involvement of drug inducibility was excluded, between 1950 and 2014. Pancolitis-type UC had a rate of 54.8% and was the most common type of UC involvement. The large intestinal mucosa damaged by UC played an important role in the onset of AIHA, and the larger the area of damaged mucosa, the more likely a complication with AIHA. Most cases (86.8%) were in the active stage of UC at the onset of AIHA. However, the remaining large intestinal mucosa in our case showed no clear findings in lower gastrointestinal tract endoscopy. Patients who developed AIHA during the course of UC account for 92.9% of all cases, and the median time from the onset of UC to the onset of AIHA was 4.3 years (range: 0 to 30 years). All except one patient (98.2%) received steroid therapy, 38.6% received an immunosuppressant such as azathioprine, 26.3% underwent splenectomy, and 29.8% received total abdominal colectomy. The remission rates after treatment were 89.2% for UC and 92.2% for

AIHA.

Only 3 of the 66 reported cases of AIHA associated with UC developed AIHA after total abdominal colectomy. Keene et al. described 2 patients with AIHA that developed AIHA at 11 and 15 years after colectomy: one achieved remission with steroid therapy, and the other died due to AIHA (9). Alonso et al. mentioned one patient with AIHA that developed AIHA immediately after total abdominal colectomy for UC; this patient died due to a pulmonary embolism (10). Since AIHA developed during the active phase of UC in most of the 66 cases, prior to possible total abdominal colectomy, it appears that the onset of AIHA as a complication of UC has an important role in the large intestinal mucosa. However, it should be noted that AIHA may occur even after an extended period after total abdominal colectomy. The present case indicates that alternative mechanisms of autoantibody production by erythrocytes may exist, since AIHA seems to have been triggered by PV-B19 infection.

PV-B19 is a single-stranded linear DNA virus of 5,596 bp that is a well-known cause of slapped cheek disease. Older children and adults with slapped cheek disease are not erythrogenic, but complain of joint pain. Erythrocyte membrane P antigen is a cellular receptor for PV-B19, and PV-B19 replicates in erythroblasts. $\alpha 5 \beta 1$ integrin is necessary for cellular invasion of PV-B19 (13, 14), and thus erythroid progenitors expressing P antigen and $\alpha 5 \beta 1$ integrin are infection targets, and this commonly causes transient pure red cell aplasia. In particular, in patients with chronic hemolytic anemia, including AIHA, a decrease in the hematopoietic capacity of red blood cells induced by initial PV-B19 infection causes an aplastic crisis (15).

It is unlikely that an aplastic crisis developed in our patient due to the onset of PV-B19 infection-induced AIHA because neither spherocytosis nor anemia developed; the LDH level was not increased; and there was no complication of chronic hemolytic anemia. It is difficult to explain why PV-B19 infection caused AIHA without the development of pure red cell aplasia. The patient may have developed AIHA because he was susceptible to a complication of autoimmune disease, including UC, for reasons other than undergoing total abdominal colectomy; however, this remains speculative. The only similar case was reported by Hirota et al. (16) for a patient who developed Evans syndrome through PV-B19 infection. This patient was positive for PV-B19 IgM and PV-B19 DNA; an initial PV-B19 infection was involved in the onset of AIHA; and hemocyte membrane antigenicity was probably modified by the virus, which could induce autoantibody production (16).

Musaji et al. hypothesized that hemolysis in AIHA requires two consecutive steps according to the results in a murine AIHA model (17). In the first step, autoantibody production in the blood cells is mediated. Secondary stimulation, such as that by a viral infection, involves cytokine secretion from immune cells to facilitate the engulfment of autoantibody-associated erythrocytes. Consistent with this hypothesis, Arner et al. described a patient with UC who de-

veloped AIHA after contracting a respiratory infection (18). In this case, using the hypothesis suggested by Musaji et al. (17), the primary stimulation of autoantibodies produced by UC as a preexisting disease was followed by cytokine secretion induced by a respiratory infection as a secondary stimulation, and these effects then facilitated the engulfment of autoantibody-associated erythrocytes. In this way, patients with UC may develop AIHA. Likewise, in addition to UC as the primary stimulation, AIHA may be induced by PV-B19 infection as a secondary stimulation; therefore, the current case may be important in establishing the relationship between UC and AIHA.

Spontaneous remission of AIHA associated with UC did not occur in the 66 previously reported cases. Roumier et al. (19) found that only 3.3% of patients with common AIHA did not require treatment, and that approximately half of healthy adults with warm AIHA that developed following an initial cytomegalovirus infection attained spontaneous remission in the follow-up (20). In AIHA induced by a viral infection, the rate of spontaneous remission with decreased infection is likely to be high. In the course of PV-B19 infection, symptoms become less severe 1 to 2 weeks after the onset of erythema and aplastic crisis in many cases (21). Our patient also achieved spontaneous remission with a similar course of PV-B19 infection, which supports the development of AIHA due to an initial PV-B19 infection. However, none of the previous cases are similar to our patient, and further investigation of spontaneous remission in a greater accumulation of cases is warranted.

We herein presented a rare case of AIHA caused by an initial infection of PV-B19 after total abdominal colectomy for UC.

The authors state that they have no Conflict of Interest (COI).

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