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【 CASE REPORT 】

Acute Exacerbation of Anemia with Parvovirus B19 Infection One Year after Sleeve Gastrectomy for Severe Obesity

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Abstract:
Pancytopenia due to malnutrition sometimes occurs after gastric bypass but is rare after sleeve gastrectomy. A 35-year-old patient underwent sleeve gastrectomy for severe obesity. Twelve months after the operation, rapid progression of macrocytic anemia with leukopenia and thrombocytopenia occurred, and a decrease in some vitamins and trace elements due to an insufficient food intake was also detected. Haptoglobin decreased, suggesting the presence of hemolysis. In addition, IgM antibody against parvovirus B19 was detected, followed by IgG antibody. Parvovirus B19 infection was suggested to be involved in the rapid progression of anemia in this malnourished patient after bariatric surgery.

Key words: sleeve gastrectomy, parvovirus B19, hemolytic anemia, pancytopenia, severe obesity

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Introduction

Bariatric surgery is an effective treatment against severe obesity. Currently, laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass surgery (hereinafter referred to as sleeve gastrectomy and bypass surgery, respectively) are the most commonly used bariatric surgeries worldwide (1, 2). In Japan, since 2014, only sleeve gastrectomy has been covered by health insurance, so it has been chosen as the surgical approach in more than 90% of patients undergoing bariatric surgery. The number of bariatric surgeries performed in Japan has increased significantly in recent years. Anemia and pancytopenia due to eating insufficiency and malnutrition are well-known complications after bariatric surgery. They can occur after both sleeve gastrectomy and bypass surgery, but the majority of cases are reported after bypass surgery (3-5).

Parvovirus B19 is a single-stranded DNA virus that was discovered in 1974. The virus attaches to the P-antigen receptor on the erythrocyte membrane (6, 7) and can subsequently arrest erythroblast maturation, which may cause acquired pure red cell aplasia. In addition, parvovirus B19 infection can cause an aplastic crisis in patients with chronic hemolytic anemia, such as sickle cell disease and hereditary spherocytosis (8-10).

We recently experienced a patient with severe obesity who developed pancytopenia with rapid progression of macrocytic anemia 12 months after sleeve gastrectomy. A decrease in vitamins and trace elements due to an inappropriate food intake was considered one of the causes of the pancytopenia, including the macrocytic anemia. In addition, acute infection with parvovirus B19 was also detected, accompanied by findings of hemolytic anemia. To our knowledge, this is the first report of acute progression of anemia with parvovirus B19 infection after sleeve gastrectomy.

Case Report

At the time of sleeve gastrectomy, the patient was 35 years old. She had grown up and lived as a woman and had been obese since childhood; at 20 years old, she weighed

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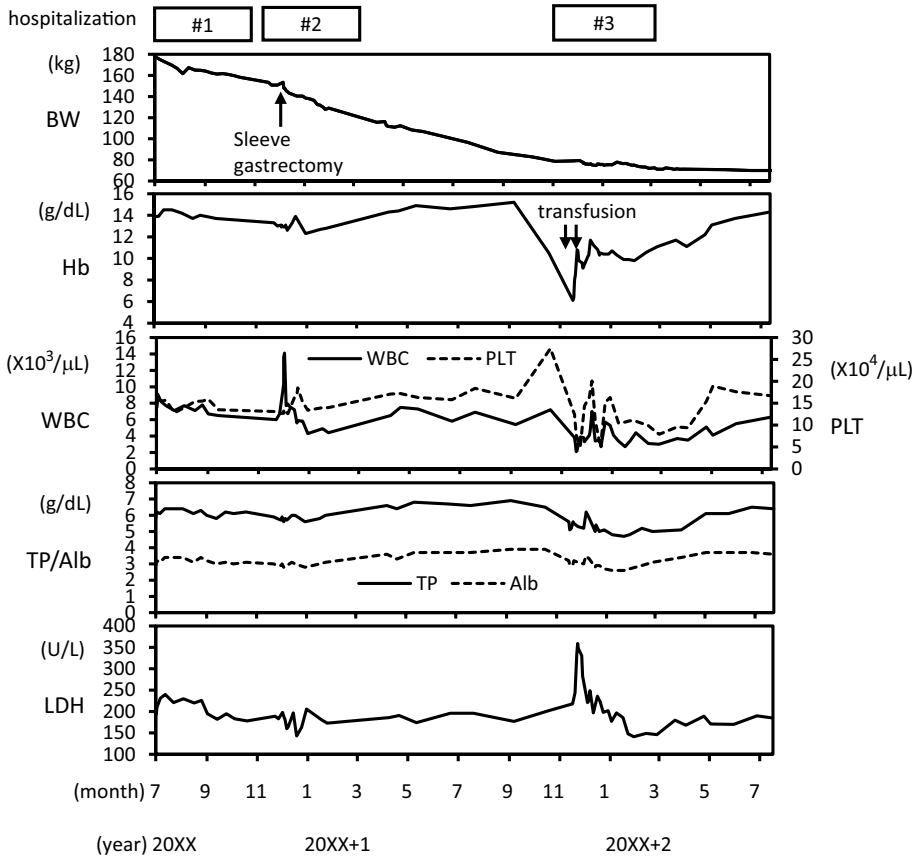

Figure. **Clinical course. Twelve months after sleeve gastrectomy, the patient developed pancytopenia with rapid progression of macrocytic anemia. Hospitalization #1: The patient received medical treatment for weight loss. Hospitalization #2: After sleeve gastrectomy, the patient continued rehabilitation. Hospitalization #3: After treatment for anemia, the patient participated in nutritional management.**

110 kg. She developed acute low back pain at 28 years old and since then she had been unable to walk, instead crawling at home. At 33 years old, she was admitted to our hospital to investigate the causes of primary amenorrhea and severe obesity. Her body weight at admission was 178 kg, which was her maximum lifetime weight. She was diagnosed with testicular feminization syndrome (chromosome 46, XY) and type 2 diabetes but secondary obesity was denied. She hoped to undergo bariatric surgery in order to return to her original social life. After about 4 months of medical treatment, she had lost 21 kg and weighed 157 kg. No obvious abnormalities were found in nutritional indicators, including albumin levels (Figure). An examination by a psychiatrist before the surgical treatment showed no obvious mental illness.

Sleeve gastrectomy was performed after the medical treatment. After the operation, the patient followed the post-surgery protocol, which consisted of meals, an oral intake of protein powder and multivitamin and mineral preparations, and rehabilitation, such as walking training. She gradually became able to stand up and walk by herself and eat normal foods orally. She was discharged home 103 days after the operation, when she weighed 116 kg (Figure).

After discharge, the patient visited our obesity outpatient clinic once a month, and in addition to seeing a doctor and undergoing laboratory tests, she received regular nutritional guidance from a dietitian. She was instructed to consume protein powder and vitamin and mineral supplements. However, her adherence to the instructions was poor, and she discontinued the oral intake of the prescribed vitamin preparation. In addition, her food intake was insufficient because of nausea and her anxious and depressive mental state. Consequently, the patient's weight loss progressed faster than expected and her weight continued to decrease by about 8 kg every month.

In the first 10 months, she had no obvious abnormalities on blood examinations, including the serum albumin level and blood count, and showed no clear signs of malnutrition (Figure). However, at a blood examination 11 months after the operation, mild anemia was found, as follows: red blood cell count, 3.2×10^6/μL; hemoglobin concentration, 10.5 g/dL; mean corpuscular volume (MCV), 97.8 fL; mean corpuscular hemoglobin (MCH), 32.8 pg; and mean corpuscular hemoglobin concentration (MCHC), 33.5 g/dL. No abnormalities were reported in white blood cells or platelets (white blood cell count, 7,200/μL; platelet count, 275×10^3/μL).

At 12 months after the operation, the patient had lost a

Table. Laboratory Findings at the Most Recent Admission.

Hematology		TP	5.6 g/dL	Folic acid	1.8 ng/mL
WBC	3,800 /μL	Alb	3.2 g/dL	Selenium	8.3 μg/dL
Neutrophils	85.9 %	UN	15.4 mg/d	Erythropoietin	14.5 mIU/mL
Eosinophils	0.5 %	Na	135 mEq/L	**Serology**	
Basophils	0.3 %	K	3.8 mEq/L	CRP	7.46 mg/dL
Monocytes	1.9 %	Cl	98 mEq/L	FT4	1.3 ng/dL
Lymphocytes	11.4 %	UA	2.4 mg/dL	FT3	2.74 pg/mL
RBC	1.75×10^6 /μL	Cre	0.39 mg/dL	TSH	2.04 μIU/mL
Hemoglobin	6.1 g/dL	eGFR	144.8	IgG	1,035 mg/dL
Hematocrit	17.8 %	Glucose	134 mg/dL	IgA	469.1 mg/dL
MCV	101.7 fL	CK	25 U/L	IgM	26.2 mg/dL
MCH	34.9 pg	HbA1c	5.0 %	IgE	212.8 IU/mL
MCHC	34.3 g/dL	TG	90 mg/dL	C3	96.1 mg/dL
Platelet	124×10^3 /μL	HDL-C	20 mg/dL	C4	25 mg/dL
Reticulocytes	1.2 ‰	LDL-C	106 mg/dL	Rheumatoid factor	-3.5 IU/mL
Coagulation		Transthyretin	5.0 mg/dL	PA-IgG	68 ng/10^7 cells
PT-INR	1.12	Transferrin	137 mg/dL	Parvovirus B19 IgM	(+)
APTT	32.6 s	BNP	13.6 pg/mL	EBV VCA IgG	40
D-Dimer	1.5 μg/mL	Ferritin	313 ng/mL	EBV VCA IgM	-10
Biochemistry		TIBC	196 μg/dL	EBV EBNA	20
AST	12 U/L	Fe	177 μg/dL	Haptoglobin	-10 mg/dL
ALT	7 U/L	Cu	118 μg/dL	Bence-Jones protein	(-)
ALP	199 U/L	Zinc	49 μg/dL	sIL-2 receptor	514 U/mL
LDH	359 U/L	Thiamine	7 ng/mL	**One month later**	
GGT	11 U/L	Riboflavin	32.6 ng/mL	Parvovirus B19 IgM	(-)
T-Bil	1.6 mg/dL	Vitamin B12	170 pg/mL	Parvovirus B19 IgG	(+)

total of 100 kg (Figure). At the same time, pancytopenia progressed rapidly, as follows: red blood cell count, 1.75×10^6/μL; hemoglobin concentration, 6.1 g/dL; MCV, 101.7 fL; MCH, 34.9 pg; MCHC, 34.3 g/dL; white blood cell count, 3,800/μL; and platelet count, 124×10^3/μL. The patient was hospitalized on the same day for a detailed examination and treatment of pancytopenia.

At this admission, massive bleeding was suspected because of the rapid progression of anemia. Upper gastrointestinal endoscopy and computed tomography were performed, but no significant bleeding was detected. On the first and third days after admission, 4 units of packed red blood cells were transfused, for a total of 8 units; on the fifth day, hemoglobin had recovered to 10.8 g/dL. Erythrocytes were mildly enlarged, and serum levels of some vitamins and trace elements were significantly decreased, including vitamin B12 (170 pg/mL), folic acid (1.8 ng/mL), zinc (49 μg/dL), and selenium (8.3 μg/dL) (Table). Therefore, malnutrition, in particular insufficient intake of vitamins and trace elements after sleeve gastrectomy, was considered to be at least one of the causes of the rapidly progressing pancytopenia. The patient started supplementation of vitamins and trace elements that had abnormally low levels. Reticulocytes increased from 1.2‰ at admission to 6.0‰ about 2 weeks after starting the supplementation, and the hemoglobin concentration was maintained at 10-11 g/dL (Figure).

In parallel with treatment, we searched for the causes of the pancytopenia with rapidly progressing macrocytic anemia. Before hospitalization, there were no new prescriptions of drugs that might cause pancytopenia. The search indicated that, in addition to the deficiencies of vitamins and trace elements, multiple factors were involved. Because erythrocytes were only mildly enlarged, we suspected iron deficiency rather than vitamin B12 and folic acid deficiency. However, because the serum iron and ferritin levels were high and the transferrin level was low, iron deficiency anemia was ruled out (Table). Haptoglobin was below the measurement sensitivity, and indirect bilirubin, aspartate aminotransferase, and lactate dehydrogenase increased transiently, suggesting the presence of hemolysis. The direct Coombs test for autoimmune hemolytic anemia was negative. Furthermore, no erythrocytes expressing CD55 (-) or CD59 (-) were found, so paroxysmal nocturnal hemoglobinuria was considered unlikely. Despite severe anemia, reticulocytes had decreased to 1.2‰, suggesting the presence of hematopoietic disorders. Unfortunately, a bone marrow aspiration test could not be performed immediately after admission but was performed on the sixth day of admission, after vitamin and trace element supplementation had already begun. A microscopic examination revealed normal bone marrow, with maintenance of differentiation into three bone marrow strains. Bone marrow multiplex polymerase chain reaction to screen for the chromosomal translocations in hematological malignancies was also negative. Importantly, a blood sampling test at admission detected an IgM antibody for parvovirus B19. One month after admission, the test for

IgM antibody for parvovirus B19 was negative, but the test for IgG antibody was positive. Based on these findings, we diagnosed the patient with chronic malnutrition with reduced vitamin and trace element levels after sleeve gastrectomy combined with exacerbation of hematopoietic disorders with acute parvovirus B19 infection and transient hemolysis, resulting in the rapid progression of anemia.

Discussion

We presented a case of pancytopenia with rapid progression of macrocytic anemia with parvovirus B19 infection one year after sleeve gastrectomy for severe obesity. The cause of the rapid progression of anemia was considered to be a combination of hematopoietic disorders and transient hemolytic anemia associated with chronic malnutrition after sleeve gastrectomy and acute infection with parvovirus B19.

Hematologic complications related to malnutrition after bariatric surgery are reported more often after bypass surgery than after sleeve gastrectomy (3-5). A meta-analysis on the frequency of malnutrition-related complications after both procedures revealed that anemia, iron deficiency anemia, iron/ferritin deficiency, and vitamin B12 deficiency were less frequent after sleeve gastrectomy than after bypass surgery (11). Although the present patient underwent sleeve gastrectomy, her vitamin B12 and folic acid levels were significantly reduced. In addition, vitamin deficiency and the associated anemia developed relatively early, i.e. one year after surgery. Because vitamin B12 is abundantly stored in the liver, megaloblastic anemia often develops several years after surgery, even if the stomach is completely removed (12). Therefore, we believe that our patient had a chronic vitamin deficiency before the sleeve gastrectomy and that her vitamin intake remained insufficient after the operation. The patient was living with her elderly, unemployed father and had been unable to stand up because of back pain for six years before hospitalization. Consequently, she had great difficulty shopping and cooking. Humans can only obtain vitamin B12 from animal-based foods, such as meat, eggs, and dairy (12). Although the patient was consuming enough calories to remain severely obese, she may not have been able to consume enough foods containing vitamins and trace elements, such as animal foods, for a long time due to familial and economic reasons. We regret that we were unable to replenish the required amounts of vitamins and trace elements during the preoperative hospitalization.

In addition, after sleeve gastrectomy, the patient's food intake was insufficient, such as because of nausea; consequently, the patient's weight loss progressed more rapidly than expected. The patient was instructed to take vitamin and trace element preparations by a dietitian, but she discontinued the oral intake of the prescribed vitamin preparation. It was also associated with the fact that her anxious and depressive mental state deteriorated after she was told about the diagnosis of testicular feminization syndrome. For these reasons, malnutrition was assumed to have occurred relatively early after the bariatric surgery. Although relatively few reports have been published on severe malnutrition after sleeve gastrectomy, malnutrition-related complications may still occur, depending on the nutritional intake before and after surgery, as they do after total gastrectomy or bypass surgery.

Anemia associated with malnutrition after bariatric surgery includes megaloblastic anemia with vitamin B12 and folic acid deficiency, zinc deficiency anemia, and iron deficiency anemia (11, 13). In our patient, serum iron exceeded the standard value, suggesting impaired iron utilization. In contrast, supplementation with vitamins and trace elements improved the erythrocyte count and normalized MCV and MCH, suggesting that the deficiency of these nutrients was involved, at least in part, in the development of anemia. In megaloblastic anemia, deficiency of vitamin B12 and folic acid impairs DNA synthesis and cell division, resulting in erythroblast enlargement (14). However, because erythrocytes were only mildly enlarged in our patient, a mitotic disorder of erythroblasts due to vitamin deficiency was considered not to be the only cause of anemia. In addition, the serum zinc level was low at admission. Zinc deficiency can induce normocytic anemia by disturbing erythroblast differentiation and proliferation (15). Thus, zinc deficiency might have been associated with the pathogenesis of anemia in our patient.

The acute infection with parvovirus B19 in our patient was also considered to be one of the factors involved in the rapid progression of macrocytic anemia. An IgM antibody against parvovirus B19 was detected at admission; the test for this antibody was negative one month later, but the test for IgG antibody was positive. New infections with parvovirus B19 can occur in adults (16, 17), but their clinical signs are atypical compared with those in children (18-21). Recently, Hayakawa et al. (19) and Yaguchi et al. (21) reported that adult patients with parvovirus B19 infection have skin rash, a fever, arthritis/myalgia, and general fatigue. In addition, they also exhibit concomitant leukopenia and thrombocytopenia (19, 21). Our patient had no obvious skin rash or a fever before and after hospitalization. Because she had exacerbation of back and leg pain and fatigue after hospitalization, she was unable to maintain a sitting position and was eating food in the lateral decubitus position. These physical findings disappeared spontaneously after only a couple of weeks and were consistent with the self-liming course associated with the viral infection. She also exhibited leukopenia and thrombocytopenia 12 months after sleeve gastrectomy. Therefore, although it was not possible to exactly specify when the infection occurred, it is highly likely that the patient was infected with parvovirus B19 before her hospitalization for anemia and that parvovirus B19 infection was involved in triggering the acute progression of anemia.

Recently, Hashimoto et al. described a patient with vitamin B12 deficiency who developed parvovirus B19 infection and acute progression of macrocytic anemia, similar to our

patient. The authors suggested that parvovirus B19 infection might have triggered acute exacerbation of anemia in their patient. However, the underlying mechanisms for the acute exacerbation of anemia, including the causal relationship between vitamin B12 deficiency and parvovirus B19 infection, were unclear (22). Anemia caused by parvovirus B19 is a hematopoietic disorder. When patients with chronic hemolytic diseases, such as hereditary spherocytosis and thalassemia, develop hematopoietic disorders due to parvovirus B19 infection, their anemia is acutely exacerbated, an event referred to as an aplastic crisis. One explanation for the rapid progression of anemia in our patient might be that acute infection with parvovirus B19 caused transient hemolysis and hematopoietic disorders. Some case reports suggest that parvovirus B19 infection causes autoimmune hemolytic anemia (23-25); however, we were unable to demonstrate the presence of this type of anemia in our patient because the direct Coombs test was negative. Since we did not find any erythrocytes expressing CD55 (-) or CD59 (-), paroxysmal nocturnal hemoglobinuria was also considered an unlikely diagnosis. In addition, no abnormalities were found in erythrocyte morphology and no events were identified that could have caused acute hemolysis, such as drug exposure. However, it is highly likely that transient hemolysis occurred before admission because haptoglobin was decreased at admission and indirect bilirubin, aspartate aminotransferase, and lactate dehydrogenase were increased, although their levels all normalized within a few weeks after admission. Therefore, although the mechanism for hemolysis was unknown, hematopoietic disorders and hemolysis were considered to have occurred at the same time as parvovirus B19 infection, resulting in an acute exacerbation of anemia.

We encountered a rare case of acute progression of anemia developing along with parvovirus B19 infection one year after sleeve gastrectomy for severe obesity.

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

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