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【 CASE REPORT 】

The Impact of Human Parvovirus B19 Infection on Heart Failure and Anemia with Reference to Iron Metabolism Markers in an Adult Woman

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Abstract:
A 35-year-old woman with fever, edema and rash was admitted. Pleural effusion and cardiomegaly were observed. A laboratory analysis revealed anemia with iron deficiency and elevated human parvovirus B19 (B19V) immunoglobulin M. The patient's hepcidin-25 and erythroferrone levels were not elevated compared to those observed later in her clinical course. On the other hand, her growth differentiation factor-15 (GDF-15) levels were elevated. She was diagnosed to have heart failure symptoms and anemia with specific iron metabolism abnormalities due to a B19V infection. After providing supportive treatment, the heart failure symptoms disappeared and her anemia had improved. This case emphasizes the need to include a B19V infection in the differential diagnosis when we encounter cases demonstrating reversible heart failure with anemia.

Key words: human parvovirus B19, heart failure, anemia, growth differentiation factor-15, erythroferrone, hepcidin-25

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Introduction

Human Parvovirus B19 (B19V) is best known for causing the childhood disease, erythema infection. Non-typical variety clinical symptoms, which are fever, headache, malaise, erythema, and arthritis, are often observed in cases of primary adult infection. Infected patients obtain lifelong immunity, and the immunoglobulin G (IgG) antibody positivity rate of B19V in adults is 80% (1). However, adults as well as children are can also infected during an epidemic season. Among Japanese adults, the B19V infection has been prevalent since 2015.

We recognized that B19V induces dilated cardiomyopathy, and myocarditis, and pure red cell aplasia even in healthy adults (2-6). Moreover, B19V binds to the receptor of erythroid progenitor cells (7), and induces the apoptosis of erythroid progenitor cells, which can lead to severe anemia (8). Because erythroid progenitor cells secrete iron homeostasis proteins, B19V may thus affect the iron metabolism. However, there is almost no research concerning iron metabolism abnormalities associated with B19V infection.

We herein report the case of a Japanese adult woman presenting with heart failure symptoms and anemia with specific iron metabolism abnormalities due to a B19V infection.

Case Report

A 35-year-old Japanese woman presented with fever on the end of June, 2016, and edema and rash in both lower extremities appeared. Her general condition gradually worsened. On beginning of July, she had a stomachache, nausea, and diarrhea, and was admitted to our hospital. She had a 3-year-old daughter and worked as a pharmacist. No relevant personal or family medical history was noted. Her hemoglobin (Hb) levels on mid April were 10.0 g/dL. Her blood

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Table 1. Laboratory Findings on Admission.

Blood cell count	Values	Normal range	Blood chemistry	Values	Normal range
WBC, /μL	49×10^2	$40\text{-}90\times10^2$	TP, g/dL	5.9	6.7-8.3
Neutrophil, %	63.1	42-74	Alb, g/dL	3.3	3.9-4.9
Lymphocyte, %	27.3	18-50	UN, mg/dL	7.1	8.0-22.0
Monocyte, %	6.9	1-8	Cr, mg/dL	0.6	0.4-0.7
Eosinophil, %	2.6	0-7	UA, mg/dL	3.8	3.0-5.5
Basophil, %	0.2	0-2	Na, mEq/L	143	135-147
RBC, /μL	276×10^4	$380\text{-}480\times10^4$	K, mEq/L	4.1	3.5-5.0
Hb, g/dL	7.6	12.0-15.2	Cl, mEq/L	110	98-108
Hct, %	24.1	35-48	Ca, mg/dL	9.1	8.8-10.2
MCV, fL	87.3	89-99	P, mg/dL	3.3	2.5-4.5
MCH, pg	27.5	29-46	AST, U/L	25	13-33
MCHC, %	31.5	31-36	ALT, U/L	25	6-27
Plt, /μL	10.4×10^4	$14\text{-}34\times10^4$	γ-GTP, U/L	23	10-47
Reticulocyte, %	3.0	0.1-2.6	ALP, U/L	151	115-359
			LDH, U/L	213	119-229
Serological test			T-Bil, mg/dL	0.7	0.2-1.2
IgG, mg/dL	1,156	820-1,740	CPK, U/L	24	45-163
IgA, mg/dL	103	90-400	Glu, mg/dL	85	70-110
IgM, mg/dL	125	52-270	Fe, μg/dL	18	43-172
ASO, IU/mL	29	lower 240	UIBC, μg/dL	232	137-325
RF, IU/mL	7	lower 15	TIBC, μg/dL	250	251-398
ANA, times	160	lower 40	TSAT, %	7.2	over 25
C3, mg/dL	64	80-140	Ferritin, ng/mL	33.9	5-157
C4, mg/dL	14.0	11.0-34.0	CRP, mg/dL	0.28	lower 0.30
CH50, U/mL	13	30-45			
EPO, mIU/mL	46.6	4.2-23.7	Urinalysis		
TSH, μIU/mL	2.16	0.50-5.00	Protein	-	-
fT3, pg/mL	2.92	2.30-4.00	Occult blood	-	-
fT4, ng/dL	1.47	0.90-1.70			
B19					
IgM, antibody index	11.1	lower 0.8			
IgG, antibody index	10.2	lower 0.8			

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Plt: blood platelet, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, ASO: anti-streptolysin O antibody, RF: rheumatoid factor: ANA: anti-deoxyribonucleic acid antibody titer, C3: complement C3, C4: complement C4, CH50: complement homolytic complement activity, EPO: erythropoietin, TSH: thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: thyroxin fT4, B19: human Parvovirus B19, TP: total protein, Alb: albumin, UN: blood urea nitrogen, Cr: creatinine, UA: uric acid, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, P: inorganic-phosphate, AST: aspartate transaminase, ALT: alanine transaminase, γ-GTP: γ-glutamyltransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, CPK: creatine phosphokinase, Glu: glucose, Fe: iron, UIBC: unsaturated iron binding capacity, TIBC: total iron binding capacity, TSAT: transferrin saturation, CRP: C-reactive protein

pressure at admission was 99/57 mmHg, her body temperature was 37.1°C, her pulse rate was 69 beats/minute, and her saturation of arterial blood oxygen in room air was 98%. Her conjunctiva was pale. Her breath and heart sounds were normal. Laboratory data are shown in Table 1. Among the findings, Hb (7.6 g/dL), hematocrit (24.1%), blood platelet (10.4×10^4/μL), transferrin saturation (7.2%), ferritin (33.9 ng/mL), complement C3 (64 mg/dL), complement hemolytic activity (CH50) (13 U/mL), and high sensitivity troponinn T (hsTnT) were notably decreased. The reticulocyte and erythropoietin levels were within the normal range. Results for N-terminal pro-brain natriuretic peptide (NT-proBNP), anti-deoxyribonucleic acid antibody titer, B19V immunoglobulin M (IgM) and IgG were increased. Tests for urinary protein and urinary occult blood yielded negative results. Plain chest radiography showed dull costophrenic angles on both sides, and the cardiothoracic ratio was 50% (Fig. 1). An electrocardiogram showed a normal sinus rhythm with incomplete right bundle branch block and a low voltage in limb leads. Computed tomography (CT) and ultrasound revealed interlobular septal thickening, pleural effusion, edematous wall thickening of the gall bladder (Fig. 2), ascites

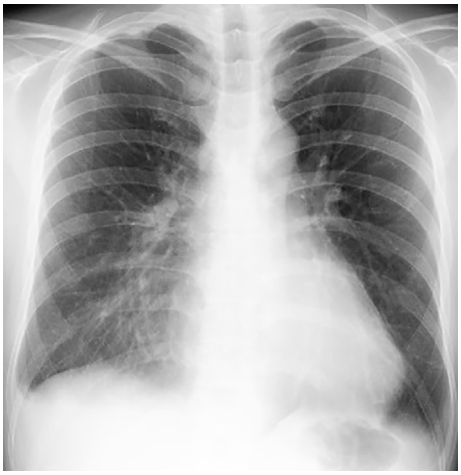

Figure 1. **Plain chest radiography: Pleural effusion and cardiomegaly are shown.**

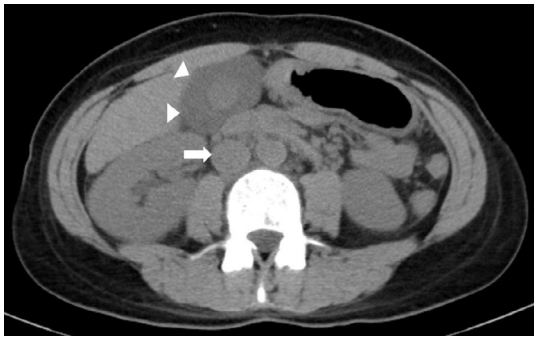

Figure 2. **Abdominal computed tomography (CT): Inferior vena cava dilatation (the arrow) and edematous wall thickening of the gall bladder (the arrow heads) are indicated.**

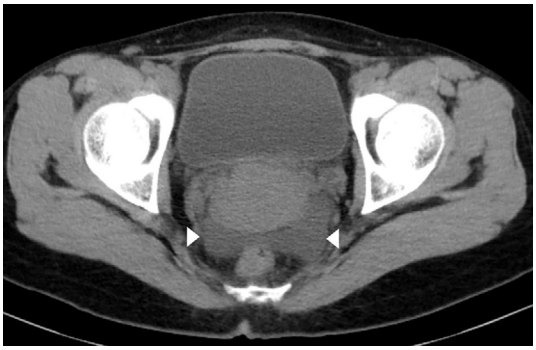

Figure 3. **Abdominal CT: The ascites are indicated by the arrows.**

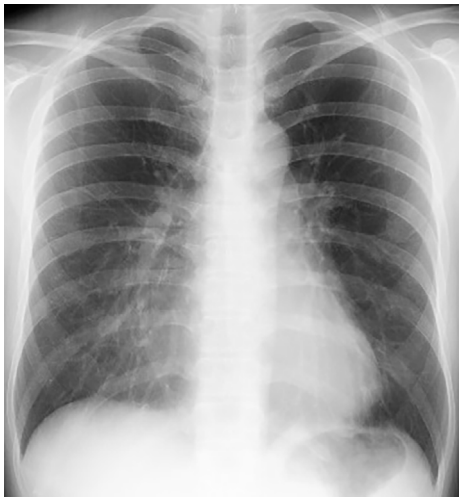

Figure 4. **Plain chest radiography: Pleural effusion and cardiomegaly have disappeared.**

(Fig. 3) and splenomegaly. Magnetic resonance imaging of the pelvis did not show any other abnormalities. Transthoracic echocardiography did not show a deterioration of the heart function, left ventricular cavity enlargement, or valvular diseases (ejection fraction 72%, fractional shortening 41%, left ventricular internal dimension in diastole 45.9 mm, and inferior vena cava 16.2 mm). On the basis of these findings, we diagnosed acute heart failure symptoms and severe anemia with iron deficiency, which were affected by a B19V infection. Intravenous 40 mg saccharated ferric oxide and 40 mg furosemide were administered to treat the anemia and fluid overload. Her urine volume was greater than 2,000 mL/day, her body weight decreased from 55.5 kg to 52.5 kg, and moreover, her leg edema disappeared. Chest radiography showed sharp costophrenic angles on both sides and the cardiothoracic ratio was 43.8% (Fig. 4). Moreover, the Hb levels increased from 7.6 g/dL to 9.6 g/dL. On the seventh hospital day, she was discharged. The major following data are shown in Table 2; on day 78, the titer of antibody index of human B19 IgM disappeared and the anemia had also improved.

For further investigation of the iron metabolism, we measured the levels of Hepcidin-25 using a Hepcidin-25 enzyme-linked immunosorbent assay (ELISA) kit (Peninsula Laboratories International, San Carlos, USA), erythroferrone using Human FAM132B ELISA kit (LifeSpan BioSciences, Seattle, USA) and growth differentiation factor-15 (GDF-15) using a Quantikine Human GDF-15 ELISA Kit (R&D Systems, Minneapolis, USA) with the patient's frozen serum. The hepcidin-25 and erythroferrone levels were not upregulated compared to those that appeared later in her clinical course. On the other hand, the GDF-15 levels were elevated (Table 2).

Discussion

This patient presented the reversible heart failure symptoms cured with only symptomatic treatment. Although the detailed mechanism of myocardial injury is unknown, dilated cardiomyopathy and myocarditis are known to occur with B19V infection (2, 3, 5, 6). However, transthoracic echocardiography did not show a deterioration of the heart function or left ventricular cavity enlargement at the time of admission. B19V binds to the receptor of vascular endothe-

Table 2. The Clinical Course of the Laboratory Findings after Discharge.

Times	on admission	day 23	day 50	day 78
B19 IgM, antibody index	11.07	11.24	3.62	1.21
Hb, g/dL	7.6	9.6	10.5	10.3
Plt, /μL	10.4×10^4	17.6×10^4	19.9×10^4	17.5×10^4
TSAT, %	7.2	36.6	37	11.4
Ferritin, ng/mL	33.9	81.2	74	44.3
Hepcidin - 25, ng/mL	16.0	48.2	22.8	16.5
erythroferrone, ng/mL	4.8	4.7	4.4	5.9
GDF - 15, pg/mL	601.7	319.2	317.4	385.8
NT-proBNP, pg/mL	319	155	121	189
hsTnT	<0.003	<0.003	<0.003	<0.003

B19 IgM: human Parvovirus B19 immunoglobulin M, Hb: hemoglobin, Plt: blood platelet, TSAT: transferrin saturation, GDF-15: growth differentiation factor-15, NT-proBNP: N-terminal pro-brain natriuretic peptide, hsTnT: high sensitivity troponinn T

lial cells (9, 10). Tschöpe et al. investigated 37 patients with exertional dyspnea, reduced exercise tolerance, and LV diastolic dysfunction despite preserved LV systolic contractility by endomyocardial biopsies analyses. The researchers guessed that B19V-induced endothelial dysfunction might be a possible pathomechanism underlying diastolic dysfunction (11). Lotze et al. examined inflammatory cardiomyopathy infected by B19V using immunohistochemistry methods. They reported that B19V infected the small vascular endothelial cells in heart muscle rather than cardiac muscle cells (12). In post-infectious glomerulonephritis-associated B 19V, hump-shaped sub-epithelial electron dense deposits tend to decrease, however, evidence of direct damage to endothelial cells by this virus is very apparent. Due to the presence of heart failure with fluid overload in this case, our patient should also have some myocardial injuries, such myocardial injuries might be caused by a transient endothelial cell dysfunction. In fact, hsTnT, direct damage marker of the myocardium, did not increase at admission. Interestingly, CT and ultrasound revealed remarkable edematous wall thickening of the gall bladder in this patient. The hepatic sinusoid, which flows from the gallbladder vein, is lined with endothelial cells. The B19V infection might have affected such endothelial cells. It may be necessary to further investigate further any direct damage of the endothelial cells by B19V could have induced the fluid overload without cardiac dysfunction.

Iron deficiency was evident as the cause of anemia in this patient from the findings of low transferrin saturation and low ferritin levels. However, direct damage to erythroid progenitor cells by B19V might be one of the causes of anemia. B19V binds to the receptor of erythroid progenitor cells, which has an erythrocyte P antigen in the sphingolipid called globoside (7). B19V induces the apoptosis of erythroid progenitor cells, which can lead to anemia (8). If B19V induces apoptosis of erythroid progenitor cells, then the number of reticulocytes in the blood of the patients will decrease. Reticulocytes in the blood of this patient had already increased at the time of admission. Therefore, the cytotoxicity that induces the apoptosis of erythroid progenitor cells by B19V might have disappeared by the time of admission.

There is almost no detailed research which has investigated the relationship between the heart failure and iron metabolism induced by B19. Hepcidin-25 is the only protein binding to ferroportin, adjusting the distribution density of ferroportin in the cell membrane and suppressing the supply of iron (13). In this patient, the hepcidin-25 levels were 16.0 ng/mL (reference normal range; 1.6-12.7 ng/mL) (14) and then increased 3 times with iron replacement treatment, fluctuating with levels of transferrin saturation and ferritin. Since hepcidin-25 is induced by iron storage, the hepcidin-25 levels in this patient might have been affected by the iron replacement treatment that was initiated after admission.

Since the serum level of GDF-15 increases and suppresses hepcidin-25 in the context of heart failure (15-18), this condition may cause an upregulation of hematopoiesis. In our case, the high level of GDF-15 at the time admission (601.7 pg/mL, reference normal average; 450±50 pg/mL) (15) decreased along with the decrease of NT-proBNP after treatment. On the other hand, erythroferrone is also known to be a suppressant of hepcidin-15 (19). The erythroferrone levels at the time of admission were not upregulated compared to those seen in the later clinical course. Generally, our findings imply that anemia in patients with heart failure improves by decreasing the hepcidin-25 levels while increasing the erythroferrone levels. However, erythroferrone is secreted by erythroid progenitor cells (19), the cytotoxicity of erythroid progenitor cells by B19V might have prevented the secretion of erythroferrone in this case.

As a limitation of our study, we could not examine the bone marrow findings, erythroblast volume in the bone marrow, reticulocytes, thus necessitating further study.

In conclusion, we herein reported the case of a Japanese adult woman with heart failure symptoms and anemia with specific iron metabolism abnormalities. Our case highlights the multi-complications associated with B19V infection.

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

References

1. Centers for Disease Control (CDC). Risks associated with human parvovirus B19 infection. MMWR Morb Mortal Wkly Rep **38**: 81-88, 93-97, 1989.
2. Kuethe F, Lindner J, Matschke K, et al. Prevalence of parvovirus B19 and human bocavirus DNA in the heart of patients with no evidence of dilated cardiomyopathy or myocarditis. Clin Infect Dis **49**: 1660-1666, 2009.
3. Lamparter S, Schoppet M, Pankuweit S, Maisch B. Acute parvovirus B19 infection associated with myocarditis in an immunocompetent adult. Hum Pathol **34**: 725-728, 2003.
4. Makino S, Fukuda T, Ueda A. Pure red cell aplasia due to persistent human parvovirus B19 infection in healthy adult. Nihon Naika Gakkai Zasshi **90**: 323-325, 2001 (in Japanese).
5. Lotze U, Egerer R, Tresselt C, et al. Frequent detection of parvovirus B19 genome in the myocardium of adult patients with idiopathic dilated cardiomyopathy. Med Microbiol Immunol **193**: 75-82, 2004.
6. Pankuweit S, Moll R, Baandrup U, Portig I, Hufnagel G, Maisch B. Prevalence of the parvovirus B19 genome in endomyocardial biopsy specimens. Hum Pathol **34**: 497-503, 2003.
7. Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. Science **262**: 114-117, 1993.
8. Moffatt S, Yaegashi N, Tada K, Tanaka N, Sugamura K. Human parvovirus B19 nonstructural (NS1) protein induces apoptosis in erythroid lineage cells. J Virol **72**: 3018-3028, 1998.
9. Bültmann BD, Klingel K, Sotlar K, et al. Fatal parvovirus B19-associated myocarditis clinically mimicking ischemic heart disease: an endothelial cell-mediated disease. Hum Pathol **34**: 92-95, 2003.
10. Magro CM, Crowson AN, Dawood M, Nuovo GJ. Parvoviral infection of endothelial cells and its possible role in vasculitis and autoimmune diseases. J Rheumatol **29**: 1227-1235, 2002.
11. Tschöpe C, Bock CT, Kasner M, et al. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. Circulation **111**: 879-886, 2005.
12. Klingel K, Sauter M, Bock CT, Szalay G, Schnorr JJ, Kandolf R. Molecular pathology of inflammatory cardiomyopathy. Med Microbiol Immunol **193**: 101-107, 2004.
13. Ganz T. Molecular control of iron transport. J Am Soc Nephrol **18**: 394-400, 2007.
14. Uehata T, Tomosugi N, Shoji T, et al. Serum hepcidin-25 levels and anemia in non-dialysis chronic kidney disease patients: a cross-sectional study. Nephrol Dial Transplant **27**: 1076-1083, 2012.
15. Tanno T, Bhanu NV, Oneal PA, et al. High levels of GDF15 in thalassemia suppress expression of the iron regulatory protein hepcidin. Nat Med **13**: 1096-1101, 2007.
16. Lakhal S, Talbot NP, Crosby A, et al. Regulation of growth differentiation factor-15 expression by intracellular iron. Blood **113**: 1555-1563, 2009.
17. Subramaniam S, Strelau J, Unsicker K. Growth differentiation factor-15 prevents low potassium-induced cell death of cerebellar granule neurons by differential regulation of Akt and ERK pathways. J Biol Chem **278**: 8904-8912, 2003.
18. Wang J, Xu N, Feng X, et al. Targeted disruption of Smad4 in cardiomyocytes results in cardiac hypertrophy and heart failure. Circ Res **97**: 821-828, 2005.
19. Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet **46**: 678-684, 2014.