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

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
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 (10.4×10^3/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 troponin 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

Table 1. Laboratory Findings on Admission.

| Blood cell count       | Values     | Normal range | Blood chemistry | Values     | Normal range |
|------------------------|------------|--------------|-----------------|------------|--------------|
| WBC, /μL               | 49×10^3    | 40-90×10^3   | 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               | 276×10^6   | 380-480×10^6 | 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  | 14-34×10^4   | 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    |                 |            |              |

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 hemolytic complement activity, EPO: erythropoietin, TSH: thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: thyroxin, 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

B19

IgM, antibody index 11.1 lower 0.8

IgG, antibody index 10.2 lower 0.8
(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 endothel-
The number of reticulocytes in the blood of the patients will be increased if B19V induces 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.

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

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