Clinical Case Report

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Parvovirus B19 infection presenting with neutropenia and thrombocytopenia

Three case reports

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Abstract

Rationale: Parvovirus B19 (PV) infection is usually symptomless and can cause benign, short-lived conditions. Anemia associated with PRCA is the most representative hematologic manifestation, but neutropenia and thrombocytopenia have been rarely reported.

Patient concerns: Three patients were admitted to the hospital with neutropenia and thrombocytopenia. The accompanying symptoms were fever, myalgia, rash, or arthralgia, and all patients were previously healthy.

Diagnosis: Patients were positive for PV PCR and diagnosed with PV infection. Before the diagnosis of PV infection, 2 patients underwent BM study and almost absence of erythroid progenitor cells in BM aspiration were a clue for the PV infection. Other BM findings were hypocellular marrow and a few hemophagocytic histiocytes.

Interventions: Patients received supportive care with follow-up of CBC.

Outcomes: All 3 patients spontaneously recovered from neutropenia and thrombocytopenia within 3 weeks without severe complications.

Lessons: The evaluation of PV infection should be considered in situations where there is neutropenia and thrombocytopenia in healthy individuals even without anemia as a differential diagnosis.

Abbreviations: BM = bone marrow, CBC = complete blood counts, PCR = polymerase chain reaction, PRCA = pure red cell aplasia, PV = Parvovirus B19.

Keywords: neutropenia, parvovirus B19, pure red cell aplasia, thrombocytopenia

1. Introduction

Parvovirus B19 (PV) is a non-enveloped, single-stranded linear DNA virus and spreads mainly through the respiratory system.[1,2] PV infection is usually asymptomatic and causes self-limiting nonspecific symptoms, such as rash, fever, myalgia, and arthralgia in healthy individuals. PV is also known to cause a variety of hematological manifestations, and pure red-cell aplasia (PRCA) is a well-known representative hematologic manifestation. In immunocompromised individuals, chronic anemia could be developed, and in patients with hereditary spherocytosis and sickle-cell disease, an anemic crisis could develop.[2] Neutropenia has been infrequently reported in various clinical situations as well as in healthy individuals,[3–7] and there is limited data for PV-associated neutropenia and thrombocytopenia. Here, we describe the clinical and laboratory characteristics of 3 patients with PV infection presenting with neutropenia and thrombocytopenia.

2. Material and methods

We reviewed medical records of patients who underwent PV PCR. A list of patients with PV polymerase chain reaction (PCR) between January 2008 and September 2018 was obtained from the electronic medical records. Patients who underwent PV PCR as a follow-up study were excluded. PV PCR was done using the in-house method. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital, and written informed consent for publication was obtained from the patient or patient's parent. Among the 335 patients who underwent PV PCR, 10 patients were positive for PV PCR, and their clinical and laboratory information was reviewed (Fig. 1). Two patients were a pregnant woman and her fetus showing fetal hydrops. Four patients were admitted with profound anemia (hemoglobin, Hb; < 9.0 g/dL), and 1 patient showed isolated neutropenia (absolute neutrophil count, ANC; 1.24×10^9/L). The remaining three patients showed neutropenia and thrombocytopenia without anemia, and all of them were previously healthy. Their clinical and laboratory characteristics are described and summarized in Table 1.

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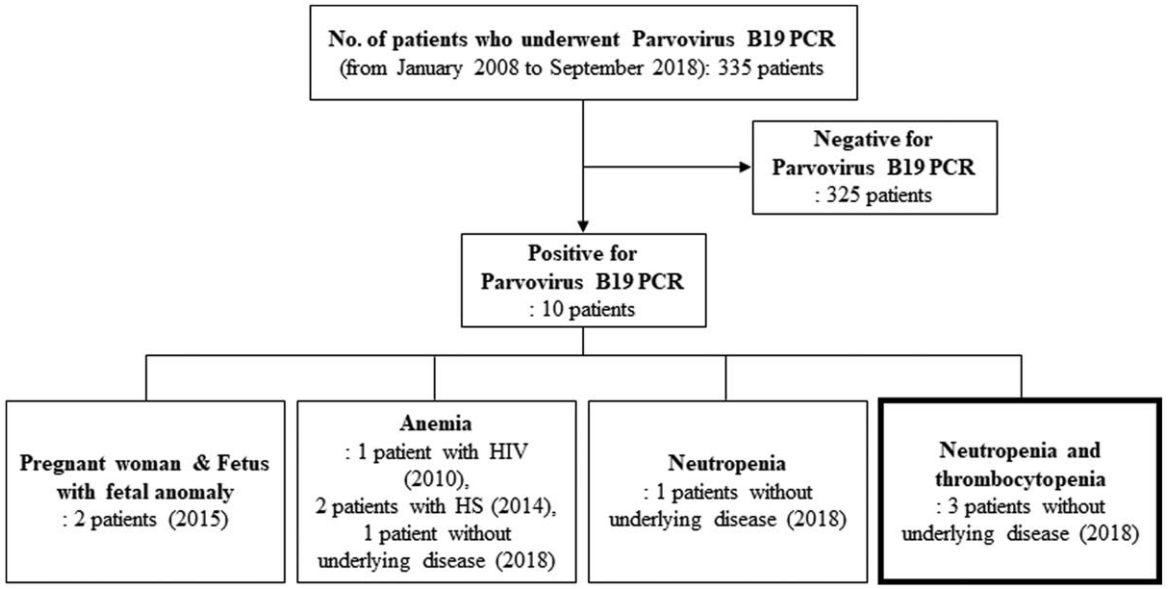

Figure 1. Schematic diagram of patients who underwent Parvovirus B19 PCR during the study period. The year that the Parvovirus B19 infection occurred is stated in parentheses. HIV = human immunodeficiency virus, HS = hereditary spherocytosis.

3. Case reports

3.1. Case 1

A 47-year-old woman was admitted to our hospital because of neutropenia and thrombocytopenia. She had a rash on both cheeks 10 days ago, and the rash was spontaneously resolved. Two days ago, mild fever, myalgia, and arthralgia were developed, and complete blood count (CBC) findings were as follows: white blood cells (WBC), 0.95×10^9/L; ANC, 0.52×10^9/L; Hb, 11.6 g/dL; platelets, 87×10^9/L; reticulocytes, 0.28%. Antinuclear antibody (ANA) was negative. Bone-marrow (BM) aspiration showed severe hypocellular particles with almost no erythroid progenitor cells and a few hemophagocytic histiocytes (Fig. 2). The BM cellularity was about 10%, which was hypocellular for her age. PV PCR was positive, and she was diagnosed with PV infection. She received supportive care, and neutropenia and thrombocytopenia recovered within 10 days (Fig. 3).

3.2. Case 2

A 37-year-old woman suffered from myalgia and fever that had started one week previously. She had the malar rash-like lesion on both cheeks, and admitted to our hospital because of neutropenia and thrombocytopenia. CBC findings were as follows: WBC, 2.92×10^9/L; ANC, 1.18×10^9/L; Hb, 14.7 g/dL; platelets, 64×10^9/L; reticulocytes, 0.07%. ANA was positive with a titer of 1:40. Anti-double-stranded DNA antibodies (anti-dsDNA) IgG and IgM were positive, and anti-cardiolipin antibodies (aCL) IgG and IgM were elevated. Anti-smith antibody and anti-beta-2 glycoprotein I antibody IgG were negative. Atypical lymphocytes were observed in the PB smear, and BM aspiration showed hypocellular particles with almost no erythroid progenitor cells and a few hemophagocytic histiocytes. The BM cellularity was 20%, which was hypocellular for her age. Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) PCR were negative, and PV PCR was positive. She received supportive care, and neutropenia and thrombocytopenia were recovered within 8 days (Fig. 3).

Table 1

Laboratory characteristics of 3 patients with neutropenia and thrombocytopenia associated with Parvovirus B19 infection.

	Age (yrs)	Sex	WBC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	Hb (g/dL)	Platelet ($\times 10^9$/L)	Reticulocyte (%)	Bone marrow findings	Immunologic findings
Case 1	46	F	0.95	0.52	11.6	87	0.28	PRCA, hypocellular marrow, a few hemophagocytosis	ANA (−)
Case 2	37	F	2.92	1.18	14.7	64	0.07	PRCA, hypocellular marrow, a few hemophagocytosis	ANA (+, 1:40); anti-dsDNA IgG/IgM (+/+); aCL IgG/IgM (elevated/elevated); anti-Sm (−); anti-β2 GP I IgG (−)
Case 3	11	M	2.4	0.35	12.3	108	0.23	n.d.	ANA (+, 1:160); anti-dsDNA IgG/IgM (equivocal/+); aCL IgG/IgM (-/elevated); aPL IgG/IgM (elevated/elevated)

aCL = anti-cardiolipin antibodies, ANA = antinuclear antibodies, ANC = absolute neutrophil counts, anti-β2 GP I = anti-beta-2 glycoprotein I antibodies, anti-dsDNA = anti-double stranded DNA antibodies, anti-Sm = anti-smith antibodies, aPL = anti-phospholipid antibodies, F = female, Hb = hemoglobin, M = male, n.d. = not done, PRCA = pure red cell aplasia, WBC = white blood cells, yrs = years.

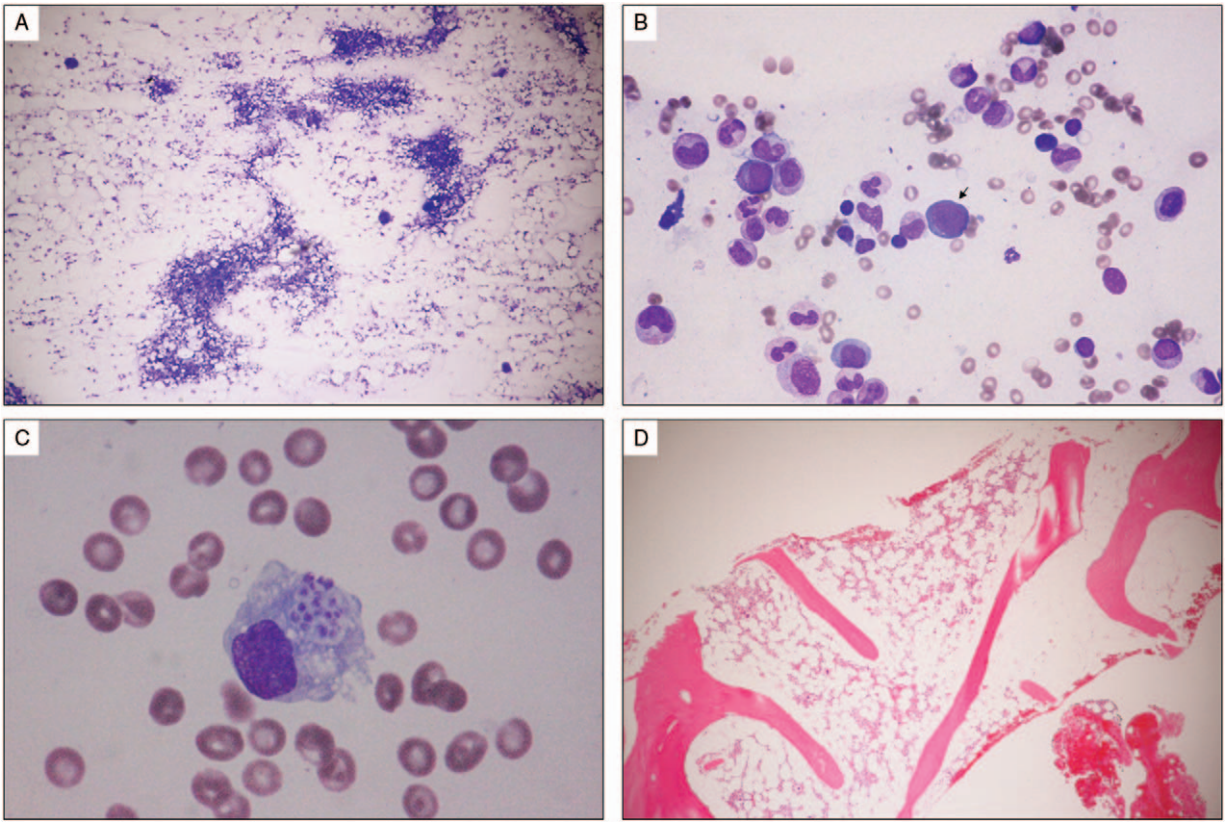

Figure 2. Bone marrow (BM) findings of Case 1. BM-aspiration smear showed (A) severe hypocellular particles, (B) a few pronormoblasts (arrow), and (C) hemophagocytic histiocytes (Wright–Giemsa stain, × 100, × 400, and × 400, respectively). (D) BM biopsy showed 10% of cellularity (Hematoxylin-eosin stain, × 100).

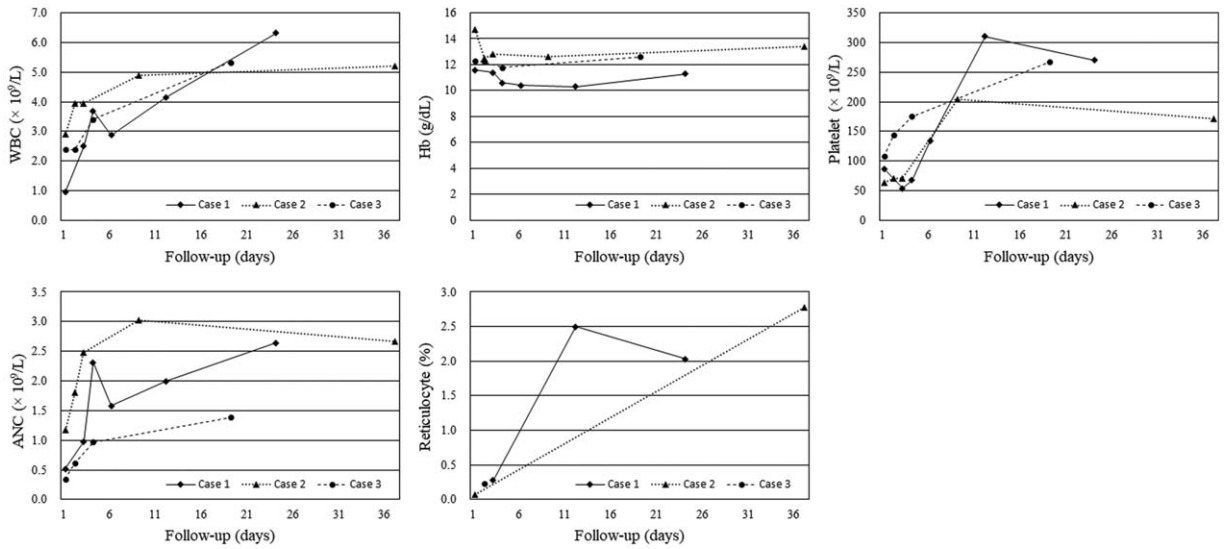

Figure 3. WBC, Hb, platelet, ANC, and reticulocyte changes in 3 patients with Parvovirus B19-associated neutropenia and thrombocytopenia during the follow-up period. ANC = absolute neutrophil counts, Hb = hemoglobin, WBC = white blood cells.

3.3. Case 3

An 11-year-old boy visited the hospital because of a petechial rash that had started 4 days ago. A fever over 38.5°C and arthralgia on the right ankle and left hip joint had developed 1 day before. On physical examination, a cervical lymph-node enlargement of about 1 cm was found. Severe neutropenia and thrombocytopenia were observed from the following CBC findings: WBC, 2.4×10^9/L; ANC, 0.35×10^9/L; Hb, 12.3 g/dL; platelets, 108×10^9/L; reticulocytes, 0.23%. ANA was positive with a titer of 1:160. Anti-dsDNA IgM was positive with an equivocal result of anti-ds DNA IgG. The aCL IgG was normal, and aCL IgM and anti-phospholipid antibodies (aPL) IgG and IgM were elevated. CMV IgM and EBV VCA IgM were negative. PV PCR was positive, and he received supportive care

for fever and arthralgia. The neutropenia and thrombocytopenia spontaneously recovered within 18 days (Fig. 3).

4. Discussion

In this study, the severity of neutropenia was varied among the 3 patients: at initial admission, they showed mild (ANC; $1.0–1.5 \times 10^9$/L), moderate ($0.5–1.0 \times 10^9$/L), and severe neutropenia ($<0.5 \times 10^9$/L), respectively. For the thrombocytopenia, 1 patient showed mild thrombocytopenia ($100–140 \times 10^9$/L) and the others showed moderate thrombocytopenia ($50–100 \times 10^9$/L). During the follow-up period, the ANC and platelet counts rapidly increased and completely recovered within 3 weeks without significant complications in all patients. All patients had Hb levels above 10 g/dL and there was no significant change in Hb levels during the follow-up period.

PV has the tropism for erythroid progenitors. Therefore, PV infects and destroys the erythroid progenitor cells in BM, leading to a drop in circulating reticulocytes.[1] Indeed, we suspected PV infection in 2 adult patients because of the BM finding of PRCA. In patients with increased RBC destruction and a high need for RBC production, acute PV infection can cause an abrupt drop of RBC production, leading to severe anemia. Also, in immunocompromised patients, viremia persists and results in chronic or recurrent anemia.[2] However, in normal individuals, hemoglobin levels ordinarily remain stable because the erythrocyte has a long-life span.

The mechanism of PV-associated neutropenia and thrombocytopenia is unclear to date. However, there have been several suggestions for neutropenia. Kurtzman et al found the replicating PV DNA in circulating cells mainly composed of mature granulocytes and suggested the direct infection of myeloid progenitors as a mechanism for the neutropenia.[8] Also, PV itself may be cytotoxic to non-erythroid cells because of the cytotoxic activity of nonstructural regulatory protein, NS1 of PV. Seo et al showed a high band-to-segmented neutrophil ratio in BM examination of patients with PV-associated neutropenia, suggesting the maturation arrest on the terminal stage of granulocytic lineage as one of the causes.[9] In our study, the maturation arrest of granulocytes was not observed in BM examination performed in 2 patients. The mechanism of thrombocytopenia was also considered to be similar to that of neutropenia. In an in vitro study, PV suppressed megakaryocyte colony formation, suggesting that PV may be cytotoxic to a megakaryocytic population without viral replication,[10] and Bhattacharyya et al reported a patient with PV-induced acquired pure amegakaryocytic thrombocytopenia.[11] In our cases, hypocellular marrow and a few hemophagocytosis were shown along with typical PRCA finding. Therefore, as a cause of neutropenia and thrombocytopenia, we considered the cytotoxic activity of PV against non-erythroid precursors as well as erythroid progenitor cells, causing transient BM suppression.

Interestingly, in our study, ANA was detected in 2 patients, and they also showed positive results for additional immunologic studies such as anti-dsDNA, aCL and/or aPL (Table 1). Especially, in 1 patient (Case 2) with a rash on both cheeks, these results led to suspicion of systemic lupus erythematosus (SLE), but the diagnostic criteria for SLE were not met. PV has been reported to be associated with production of various autoantibodies including anti-dsDNA, aCL and aPL.[12] There are suggestions that PV may be involved in the pathogenesis of various autoimmune diseases, and a relationship between PV and SLE has been suggested for 3 situations of PV infection that mimicked the clinical and laboratory characteristics of SLE, exacerbated previously developed SLE, or initiated the development of SLE.[13] Therefore, clinical attention is required when lupus-like symptoms are present with PV infection.

In this study, we demonstrate the variable severities of neutropenia and thrombocytopenia in patients with PV infection. Since all patients developed a rash, this could be the one of the clues for PV-associated neutropenia and thrombocytopenia. The evaluation of PV infection should be considered in situations where there is neutropenia and thrombocytopenia in healthy individuals as a differential diagnosis.

Author contributions

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